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Veröffentlicht
Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.

(54) Title: EPOTHILONE MINOR CONSTITUENTS

(54) Bezeichnung: EPOTHILON–NEBENKOMPONENTEN

(57) Abstract

The invention relates to compounds which are obtained by fermenting DSM 6773, especially epothilones A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 and K and trans–epothilones C1 and C2.

(57) Zusammenfassung

Die Erfindung betrifft Verbindungen, die durch Fermentation von DSM 6773 erhältlich sind, insbesondere Epothilone A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 und K und Trans–Epothilone C1 und C2.

LEDIGLICH ZUR INFORMATION

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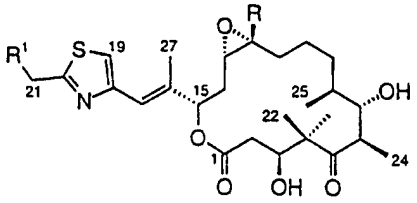
Epothilon-Nebenkomponenten

Die Erfindung betrifft Verbindungen, die im vorliegenden Zusammenhang als Epothilon-Nebenkomponenten bezeichnet werden, und zwar Verbindungen 5 bis 13 und 16 bis 39. Diese Verbindungen lassen sich durch Fermentation von DSM 6773 gemäß DE 41 38 042.8 gewinnen.

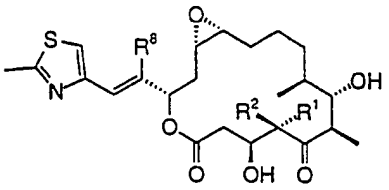
Kenndaten der erfindungsgemäßen Verbindungen sind im folgenden zusammengestellt.

Gewinnung: Die Aufarbeitung eines Rohepothilon-Gemischs, das durch Fermentation von DSM 6773 in einem 900 Liter-Fermentator gewonnen wurde, ist schematisch Fig. 1 bis 2 zu entnehmen.

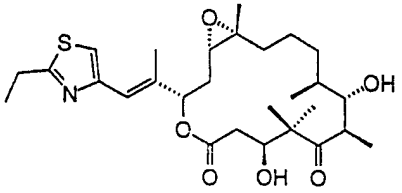
Aktivitäten: vgl. Tab. 1



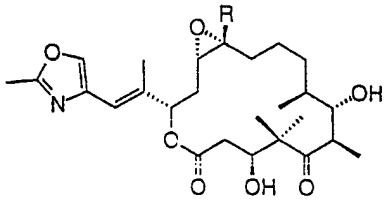
Epothilone A (1) R^1 = H; R = H
Epothilone B (2) R^1 = H; R = Me
Epothilone E (3) R^1 = OH; R = H
Epothilone F (4) R^1 = OH; R = Me



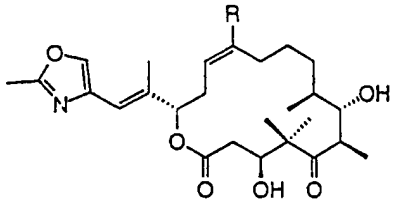
Epothilone A_1 (5) R^1 = H; R^2, R^8 = Me
Epothilone A_2 (6) R^2 = H; R^1, R^8 = Me
Epothilone A_8 (7) R^8 = H; R^1, R^2 = Me
Epothilone A_9 (8) R^1 = CH_2OH; R^2, R^8 = Me



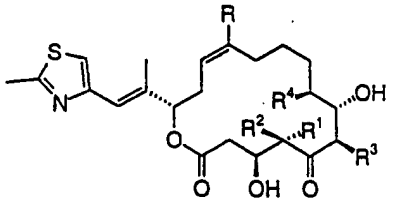
Epothilone B_{10} (9)



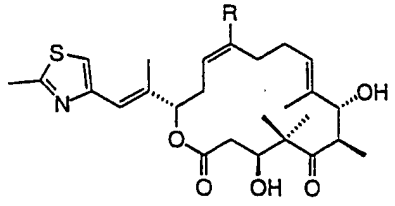
Epothilone G_1 (10) R = H
Epothilone G_2 (11) R = Me



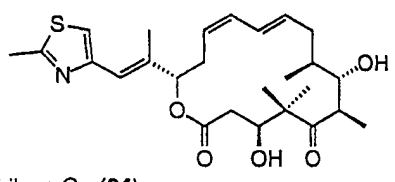
Epothilone H_1 (12) R = H
Epothilone H_2 (13) R = Me



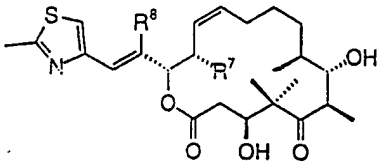
Epothilone C (14) R^1, R^2, R^3, R^4 = Me; R = H
Epothilone D (15) R^1, R^2, R^3, R^4, R = Me
Epothilone C_1 (16) R^1 = H; R^2, R^3, R^4 = Me; R = H
Epothilone D_1 (17) R^1 = H; R^2, R^3, R^4 = Me; R = Me
Epothilone C_2 (18) R^2 = H; R^1, R^3, R^4 = Me; R = H
Epothilone D_2 (19) R^2 = H; R^1, R^3, R^4 = Me; R = Me
Epothilone C_3 (20) R^3 = H; R^1, R^2, R^4 = Me; R = H
Epothilone C_4 (21) R^4 = H; R^1, R^2, R^3 = Me; R = H



Epothilone C_5 (22) R = H
Epothilone D_5 (23) R = Me



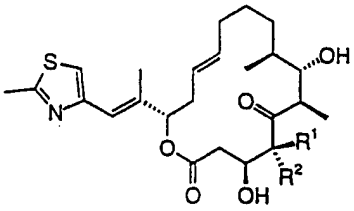
Epothilone C_6 (24)



Epothilone C_7 **(25)** $R^7 = OH$; $R^8 = Me$

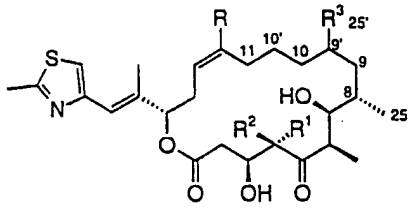
Epothilone C_8 **(26)** $R^8, R^7 = H$

Epothilone C_9 **(27)** $R^8 = CH_2OH$; $R^7 = H$



trans-Epothilone C_1 **(28)** $R^1 = H$; $R^2 = Me$

trans-Epothilone C_2 **(29)** $R^2 = H$; $R^1 = Me$



Epothilone I_1 **(30)** R, $R^3 = H$; $R^1, R^2 = Me$

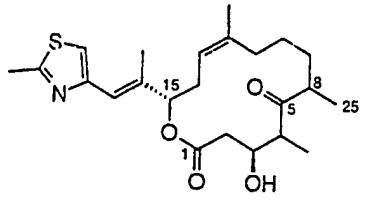
Epothilone I_2 **(31)** R = H; $R^1, R^2, R^3 = Me$

Epothilone I_3 **(32)** R^1, R^2, R^3, R = Me

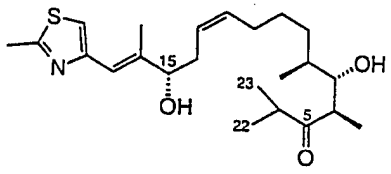
Epothilone I_4 **(33)** R^2, R = H; $R^1, R^3 = Me$

Epothilone I_5 **(34)** $R^2 = H$; R^1, R^3, R = Me

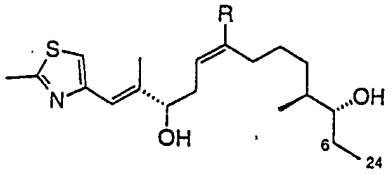
Epothilone I_6 **(35)** $R^1 = H$; R^2, R^3, R = Me



Epothilone K **(36)**



(37)



(38) R = H

(39) R = Me

Epothilone A_1 (5): colorless amorphous solid; $[\alpha]^{22}_D$ –69 (*c* 0.1, MeOH); UV (MeOH) λ_{max} nm (ε) 208 (19600), 247 (13600); IR (KBr) ν_{max} 3437, 2959, 2931, 2876, 1732, 1710, 1455, 1259, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.95 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.68 (1H, dd, *J* = 4.4, 4.0 Hz, H-15), 4.12 (1H, m, H-3), 3.71 (1H, m, H-7), 3.52 (1H, bs, 7-OH), 3.37 (1H, bd, *J* = 7.5 Hz, 3-OH), 3.21 (1H, dq, *J* = 7.7, 7.0 Hz, H-4), 3.02 (1H, ddd, *J* = 9.2, 4.5, 2.8 Hz, H-13), 2.87 (1H, ddd, *J* = 8.3, 4.5, 3.7 Hz, H-12), 2.78 (1H, dd, *J* = 16.8, 4.3 Hz, H-2a), 2.70 (3H, s, H-21), 2.66 (1H, dq, *J* = 3.9, 7.0 Hz, H-6), 2.65 (1H, dd, *J* = 16.8, 5.2 Hz, H-2b), 2.16 (1H, ddd, *J* = 15.4, 4.4, 2.8 Hz, H-14a), 2.12 (3H, bs, H-27), 1.91 (1H, ddd, *J* = 15.4, 9.2, 4.0 Hz, H-14b), 1.63 (1H, m, H-10a), 1.62 (2H, m, H-11), 1.59 (1H, m, H-9a), 1.52 (1H, m, H-10b), 1.39 (1H, m, H-8), 1.35 (1H, m, H-9b), 1.211 (3H, d, *J* = 7.0 Hz, H-23), 1.207 (3H, d, *J* = 7.0 Hz, H-24), 0.89 (3H, d, *J* = 6.9 Hz, H-25); EIMS *m/z* 479 $[M]^+$ (21), 322 (31), 306 (65), 304 (47), 168 (45), 166 (73), 164 (100), 151 (30), 140 (35); HREIMS *m/z* 479.2317 (calcd. for $C_{27}H_{41}NO_5S$, 479.2342).

Epothilone A_2 (6): colorless amorphous solid; $[\alpha]^{22}_D$ +12.0 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (15100), 248 (15500); IR (KBr) ν_{max} 3438, 2963, 2929, 2875, 1734, 1706, 1458, 1262, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98 (1H, s, H-19), 6.63 (1H, bs, H-17), 5.40 (1H, dd, *J* = 8.3, 3.4 Hz, H-15), 4.26 (1H, ddd, *J* = 8.5, 4.8, 4.7 Hz, H-3), 3.85 (1H, dd, *J* = 7.9,

2.6 Hz, H-7), 3.54 (1H, bs, 3-OH), 3.09 (1H, dq, J = 4.8, 7.0 Hz, H-4), 3.01 (1H, ddd, J = 8.3, 4.8, 4.6 Hz, H-13), 2.98 (1H, dq, J = 7.9, 7.0 Hz, H-6), 2.89 (1H, ddd, J = 6.7, 4.6, 4.4 Hz, H-12), 2.68 (3H, s, H-21), 2.60 (1H, dd, J = 15.1, 8.5 Hz, H-2a), 2.52 (1H, bs, 7-OH), 2.50 (1H, dd, J = 15.1, 4.7 Hz, H-2b), 2.18 (1H, ddd, J = 15.0, 4.8,3.4 Hz, H-14a), 2.11 (3H, d, J = 1.3 Hz, H-27), 1.82 (1H, ddd, J = 15.0, 8.3, 8.1 Hz, H-14b), 1.63 (1H, m, H-8), 1.61 (2H, m, H-11a and H-10a), 1.46 (1H, m, H-11b), 1.39 (2H, m, H-9), 1.31 (1H, m, H-10b), 1.22 (3H, d, J = 7.0 Hz, H-24), 1.15 (3H, d, J = 7.0 Hz, H-22), 1.01 (3H, d, J = 6.9 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.2 (s, C-5), 170.1 (s, C-1), 164.9 (s, C-20), 152.0 (s, C-18), 137.0 (s, C-16), 120.3 (d, C-17), 116.5 (d, C-19), 76.7 (d, C-15), 75.6 (d, C-7), 69.1 (d, C-3), 57.1 (d, C-12), 54.3 (d, C-13), 50.3 (d, C-4), 49.6 (d, C-6), 39.4 (t, C-2), 35.5 (d, C-8), 32.2 (t, C-14), 29.6 (t, C-9), 27.6 (t, C-11), 23.9 (t, C-10), 19.2 (q, C-21), 18.0 (q, C-25), 15.6 (q, C-27), 13.9 (q, C-24), 12.4 (q, C-22); EIMS *m/z* 479 $[M]^+$ (18), 322 (38), 306 (78), 304 (59), 168 (48), 166 (96), 164 (100), 151 (33), 140 (38); HREIMS *m/z* 479.2318 (calcd. for $C_{27}H_{41}NO_5S$, 479.2342).

Epothilone A_5 (7): colorless amorphous solid; $[\alpha]^{22}_D$ –76.2 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (15300), 248 (15500); IR (KBr) ν_{max} 3440, 2967, 2932, 2876, 1736, 1691, 1467, 1252, 979 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.95 (1H, s, H-19), 6.64 (1H, dd, J = 15.6, 0.9 Hz, H-17), 6.52 (1H, dd, J = 15.6, 6.6 Hz, H-16), 5.68 (1H, dddd, J = 7.8, 6.6, 3.2, 0.9 Hz, H-15), 4.11 (1H, ddd, J = 10.1, 6.6, 3.5 Hz, H-3), 3.78 (1H, ddd, J = 5.2, 3.2, 3.2 Hz, H-7), 3.66 (1H, d, J = 6.6 Hz, 3-OH), 3.23 (1H, dq, J = 5.2, 6.9 Hz, H-6), 3.08 (1H, ddd, J = 7.3, 5.5 ,4.1 Hz, H-13), 2.90 (1H, ddd, J = 6.6, 4.6, 4.1 Hz, H-12), 2.69 (3H, s, H-21), 2.52 (1H, dd, J = 14.7, 10.1 Hz, H-2a), 2.44 (1H, bd, J = 3.2 Hz, 7-OH), 2.41 (1H, dd, J = 14.7, 3.5 Hz, H-2b), 2.10

(1H, ddd, J = 15.0, 5.5, 3.2 Hz, H-14a), 1.90 (1H, ddd, J = 15.0, 7.8, 7.3 Hz, H-14b), 1.71 (1H, m, H-8), 1.65 (1H, m, H-11a), 1.50 (1H, m, H-10a), 1.47 (1H, m, H-11b), 1.40 (2H, m, H-9), 1.39 (1H, m, H-10b), 1.33 (3H, s, H-23), 1.16 (3H, d, J = 6.9 Hz, H-24), 1.08 (3H, s, H-22), 0.98 (3H, d, J = 7.0 Hz, H-25); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.3 (s, C-5), 170.7 (s, C-1), 166.5 (s, C-20), 152.2 (s, C-18), 128.4 (d, C-16), 125.9 (d, C-17), 116.4 (d, C-19), 75.0 (d, C-7), 73.6 (d, C-3), 72.7 (d, C-15), 57.3 (d, C-12), 54.1 (d, C-13), 52.6 (s, C-4), 43.8 (d, C-6), 38.9 (t, C-2), 36.3 (d, C-8), 32.5 (t, C-14), 30.3 (t, C-9), 26.7 (t, C-11), 24.0 (t, C-10), 21.3 (q, C-23), 21.0 (q, C-22), 19.3 (q, C-21), 17.1 (q, C-25), 14.5 (q, C-24); EIMS *m/z* 479 $[M]^+$ XXX; HRDCIMS *m/z* 480.2401 (calcd. for $C_{25}H_{38}NO_6S$, 480.2401).

Epothilone A_9 (8): colorless amorphous solid; $[\alpha]^{22}_D$ –37.6 (*c* 0.5, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (15500), 253 (14100); IR (KBr) ν_{max} 3423, 2965, 2932, 2877, 1736, 1690, 1463, 1249, 1014, 979 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (1H, s, H-19), 6.72 (1H, dd, J = 10.7, 4.3 Hz, 27-OH), 6.60 (1H, bs, H-17), 5.69 (1H, dd, J = 11.6, 2.0 Hz, H-15), 5.59 (1H, d, J = 6.6 Hz, 3-OH), 4.49 (1H, ddd, J = 12.9, 4.3, 1.2 Hz, H-27a), 4.27 (1H, ddd, J = 11.6, 6.6, 2.9 Hz, H-3), 4.11 (1H, ddd, J = 12.9, 10.7, 1.0 Hz, H-27b), 3.71 (1H, ddd, J = 4.8, 3.0, 2.8 Hz, H-7), 3.17 (1H, dq, J = 3.0, 6.8 Hz, H-6), 3.04 (1H, ddd, J = 9.7, 3.6, 2.2 Hz, H-13), 2.93 (1H, bs, 7-OH), 2.91 (1H, ddd, J = 9.7, 3.6, 2.7 Hz, H-12), 2.72 (3H, s, H-21), 2.48 (1H, dd, J = 14.2, 11.6 Hz, H-2a), 2.11 (1H, dd, J = 14.2, 2.9 Hz, H-2b), 2.03 (1H, ddd, J = 14.7, 2.2, 2.0 Hz, H-14a), 1.86 (1H, m, H-11a), 1.85 (1H, m, H-14b), 1.79 (1H, m, H-8), 1.52 (1H, m, H-10a), 1.37 (3H, m, H-9 and H-10b), 1.37 (3H, s, H-23), 1.36 (1H, m, H-11b), 1.19 (3H, d, J = 6.8 Hz, H-24), 1.02 (3H, d, J = 7.1 Hz, H-25), 1.00 (3H, s, H-22); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.5 (s, C-5),

170.2 (s, C-1), 167.5 (s, C-20), 150.7 (s, C-18), 138.9 (s, C-16), 125.2 (d, C-17), 119.5 (d, C-19), 76.7 (d, C-15), 73.4 (d, C-7), 70.4 (d, C-3), 57.7 (d, C-12), 57.2 (t, C-27), 55.3 (d, C-13), 54.2 (s, C-4), 41.3 (d, C-6), 40.7 (t, C-2), 37.5 (d, C-8), 31.8 (t, C-14), 31.2 (t, C-9), 28.0 (t, C-11), 23.7 (q, C-23), 23.2 (t, C-10), 19.2 (q, C-21), 16.8 (q, C-22), 15.8 (q, C-25), 13.5 (q, C-24); EIMS *m/z* 509 $[M]^+$ (9), 491 (4), 322 (28), 321 (25), 180 (45), 167 (40), 166 (100), 165 (49), 154 (47), 138 (33); HREIMS *m/z* 509.2467 (calcd. for $C_{26}H_{39}NO_7S$, 509.2447).

Epothilone B_{10} (9): colorless amorphous solid; $[\alpha]_D^{22}$ **–27 (*c* 0.15, MeOH); UV** (MeOH) λ_{max} nm (ε) 212 (15800), 247 (12500); IR (KBr) ν_{max} 3434, 2962, 2930, 2876, 2858, 1733, 1692, 1461, 1259, 1052, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.99 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.42 (1H, dd, *J* = 8.0, 3.0 Hz, H-15), 4.25 (1H, ddd, *J* = 9.5, 6.3, 2.8 Hz, H-3), 4.23 (1H, bs, 3-OH), 3.77 (1H, ddd, *J* = 4.0, 3.9, 3.8 Hz, H-7), 3.30 (1H, dq, *J* = 4.0, 6.9 Hz, H-6), 3.01 (2H, q, *J* = 7.6 Hz, H-21), 2.81 (1H, dd, *J* = 7.7, 4.6 Hz, H-13), 2.68 (1H, bs, 7-OH), 2.54 (1H, dd, *J* = 13.9, 9.5 Hz, H-2a), 2.36 (1H, dd, *J* = 13.9, 2.8 Hz, H-2b), 2.11 (1H, ddd, *J* = 15.3, 4.6, 3.0 Hz, H-14a), 2.09 (3H, s, H-27), 1.91 (1H, ddd, *J* = 15.3, 8.0, 7.7 Hz, H-14b), 1.74 (1H, m, H-8), 1.73 (1H, m, H-11a), 1.51 (1H, m, H-10a), 1.41 (1H, m, H-11b), 1.39 (3H, t, *J* = 7.6 Hz, H-28), 1.38 (3H, m, H-9 and H-10b), 1.37 (3H, s, H-23), 1.28 (3H, s, H-26), 1.17 (3H, d, *J* = 6.9 Hz, H-24), 1.09 (3H, s, H-22), 1.01 (3H, d, *J* = 7.0 Hz, H-25); EIMS *m/z* 521 $[M]^+$ (22), 449 (7), 350 (18), 334 (57), 248 (16), 234 (27), 196 (41), 182 (59), 180 (96), 178 (100), 166 (44), 154 (44); HREIMS *m/z* 521.2808 (calcd. for $C_{28}H_{43}NO_6S$, 521.2811).

Epothilone G_1 (10): colorless amorphous solid; $[\alpha]^{22}_D$ –39.7 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 203 (15200), 236 (15100); IR (KBr) ν_{max} 3456, 2962, 2933, 2876, 1736,

1691, 1585, 1466, 1262, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (1H, s, H-19), 6.33 (1H, bs, H-17), 5.42 (1H, dd, *J* = 8.3, 2.9 Hz, H-15), 4.11 (1H, ddd, *J* = 10.1, 6.1, 3.4 Hz, H-3), 3.78 (1H, bddd, *J* = 5.2, 3.5, 3.5 Hz, H-7), 3.63 (1H, bd, *J* = 6.1 Hz, 3-OH), 3.21 (1H, dq, *J* = 5.2, 7.0 Hz, H-6), 3.00 (1H, ddd, *J* = 7.7, 4.8, 4.2 Hz, H-13), 2.88 (1H, ddd, *J* = 7.1, 4.2, 4.2 Hz, H-12), 2.53 (1H, dd, *J* = 14.8, 10.1 Hz, H-2a), 2.51 (1H, bd, *J* = 3.5 Hz, 7-OH), 2.43 (1H, dd, *J* = 14.8, 3.4 Hz, H-2b), 2.43 (3H, s, H-21), 2.07 (1H, ddd, *J* = 15.1, 4.8, 2.9 Hz, H-14a), 1.99 (3H, d, *J* = 1.3 Hz, H-27), 1.86 (1H, ddd, *J* = 15.1, 8.3, 7.7 Hz, H-14b), 1.71 (1H, m, H-8), 1.69 (1H, m, H-11a), 1.53 (1H, m, H-10a), 1.42 (1H, m, H-11b), 1.40 (3H, m, H-9 and H-10b), 1.34 (3H, s, H-23), 1.16 (3H, d, *J* = 7.0 Hz, H-24), 1.09 (3H, s, H-22), 0.99 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.1 (s, C-5), 170.5 (s, C-1), 161.0 (s, C-20), 137.4 (s, C-18), 136.7 (s, C-16), 135.9 (d, C-19), 116.4 (d, C-17), 76.4 (d, C-15), 74.9 (d, C-7), 73.7 (d, C-3), 57.4 (d, C-12), 54.4 (d, C-13), 52.6 (s, C-4), 43.8 (d, C-6), 38.8 (t, C-2), 36.2 (d, C-8), 31.4 (t, C-14), 30.4 (t, C-9), 27.0 (t, C-11), 23.9 (t, C-10), 21.3 (q, C-23), 21.2 (q, C-22), 17.2 (q, C-25), 15.8 (q, C-27), 14.4 (q, C-24), 13.8 (q, C-21); EIMS *m/z* 477 $[M]^+$ (4), 405 (7), 290 (40), 152 (39), 150 (100), 148 (23), 124 (23); HREIMS *m/z* 477.2684 (calcd. for $C_{26}H_{39}NO_7$, 477.2727).

Epothilone G_2 (11): colorless amorphous solid; $[\alpha]^{22}_D$ −22.6 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 202 (21500), 236 (14800); IR (KBr) ν_{max} 3456, 2965, 2934, 2877, 1737, 1690, 1586, 1464, 1250, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (1H, s, H-19), 6.33 (1H, bs, H-17), 5.43 (1H, dd, *J* = 7.1, 3.6 Hz, H-15), 4.12 (1H, ddd, *J* = 9.9, 6.4, 3.4 Hz, H-3), 3.77 (1H, ddd, *J* = 4.7, 4.4, 4.1 Hz, H-7), 3.83 (1H, bd, *J* = 6.4 Hz, 3-OH), 3.30 (1H, dq, *J* = 4.7, 6.9

Hz, H-6), 2.78 (1H, dd, J = 7.0, 5.4 Hz, H-13), 2.54 (1H, dd, J = 14.3, 9.9 Hz, H-2a), 2.51 (1H, bd, J = 4.1 Hz, 7-OH), 2.44 (3H, s, H-21), 2.40 (1H, dd, J = 14.3, 3.4 Hz, H-2b), 2.03 (1H, ddd, J = 15.2, 5.4, 3.6 Hz, H-14a), 2.00 (3H, d, J = 1.3 Hz, H-27), 1.92 (1H, ddd, J = 15.1, 7.1, 7.0 Hz, H-14b), 1.71 (1H, m, H-8), 1.68 (1H, m, H-11a), 1.51 (1H, m, H-10a), 1.42 (1H, m, H-11b), 1.39 (3H, m, H-9 and H-10b), 1.35 (3H, s, H-23), 1.26 (3H, s, H-26), 1.16 (3H, d, J = 6.9 Hz, H-24), 1.07 (3H, s, H-22), 0.99 (3H, d, J = 7.0 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.7 (s, C-5), 170.5 (s, C-1), 161.0 (s, C-20), 137.4 (s, C-18), 136.5 (s, C-16), 135.9 (d, C-19), 116.3 (d, C-17), 76.6 (d, C-15), 74.6 (d, C-7), 73.5 (d, C-3), 61.3 (s, C-12), 61.1 (d, C-13), 52.7 (s, C-4), 43.4 (d, C-6), 39.0 (t, C-2), 36.5 (d, C-8), 32.0 (t, C-11), 31.8 (t, C-14), 30.8 (t, C-9), 22.8 (t, C-10), 22.9 (q, C-26), 21.0 (q, C-23), 20.8 (q, C-22), 17.2 (q, C-25), 15.9 (q, C-27), 14.1 (q, C-24), 13.8 (q, C-21); EIMS *m/z* 491[M]$^+$ (21), 419 (6), 320 (18), 304 (39), 166 (42), 152 (57), 150 (100), 149 (44), 148 (58), 124 (35), 109 (33); HREIMS *m/z* 491.2878 (calcd. for $C_{27}H_{41}NO_7$, 491.2883).

Epothilone H_1 (12): colorless amorphous solid; $[\alpha]^{22}_D$ −84.2 (*c* 0.2, MeOH); UV (MeOH) λ_{max} nm (ε) 203 (19600), 237 (12000); IR (KBr) ν_{max} 3436, 2933, 2880, 2860, 1734, 1688, 1585, 1251, 1007 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (1H, s, H-19), 6.31 (1H, bs, H-17), 5.43 (1H, ddd, J = 10.6, 10.2, 4.5 Hz, H-12), 5.36 (1H, dddd, J = 10.6, 9.6, 5.0, 1.3 Hz, H-13), 5.30 (1H, dd, J = 9.9, 2.0 Hz, H-15), 4.16 (1H, ddd, J = 11.2, 5.3, 2.8 Hz, H-3), 3.73 (1H, ddd, J = 3.9, 2.5, 2.3 Hz, H-7), 3.12 (1H, dq, J = 2.3, 6.9 Hz, H-6), 2.92 (1H, d, J = 2.5 Hz, 7-OH), 2.91 (1H, d, J = 5.3 Hz, 7-OH), 2.66 (1H, ddd, J = 15.1, 9.9, 9.6 Hz, H-14a), 2.50 (1H, dd, J = 15.4, 11.2 Hz, H-2a), 2.43 (3H, s, H-21), 2.37 (1H, dd, J = 15.4, 2.8 Hz, H-2b), 2.23

(1H, m, H-14b), 2.18 (1H, m, H-11a), 2.01 (1H, m, H-11b), 2.08 (3H, d, J = 1.3 Hz, H-27), 1.74 (1H, m, H-8), 1.65 (1H, m, H-10a),1.33 (1H, m, H-9a), 1.31 (3H, s, H-23), 1.19 (1H, m, H-10b), 1.18 (1H, m, H-9b), 1.17 (3H, d, J = 6.9 Hz, H-24), 1.08 (3H, s, H-22), 0.99 (3H, d, J = 7.1 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 461 $[M]^+$ (6), 310 (5), 274 (10), 273 (7), 171 (63), 152 (100), 148 (18), 111 (15); HREIMS *m/z* 461.2743 (calcd. for $C_{26}H_{39}NO_6$, 461.2777).

Epothilone H_2 (13): colorless amorphous solid; $[\alpha]^{22}_D$ –44.4 (*c* 0.25, MeOH); UV (MeOH) λ_{max} nm (ε) 203 (14500), 236 (12200); IR (KBr) ν_{max} 3436, 2967, 2935, 2880, 1734, 1690, 1586, 1251, 1007 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (1H, s, H-19), 6.30 (1H, bs, H-17), 5.23 (1H, dd, J = 9.8, 2.1 Hz, H-15), 5.12 (1H, dd, J = 10.1, 5.3 Hz, H-13), 4.20 (1H, ddd, J = 10.8, 5.7, 2.9 Hz, H-3), 3.71 (1H, ddd, J = 3.8, 2.6, 2.6 Hz, H-7), 3.14 (1H, dq, J = 2.6, 6.9 Hz, H-6), 2.93 (d, J = 5.7 Hz, 3-OH), 2.90 (1H, bd, J = 2.6 Hz, 7-OH), 2.62 (1H, ddd, J = 15.1, 9.8, 9.8 Hz, H-14a), 2.46 (1H, dd, J = 15.1, 10.8 Hz, H-2a), 2.43 (3H, s, H-21), 2.32 (1H, dd, J = 15.1, 2.9 Hz, H-2b), 2.29 (1H, m, H-11a), 2.19 (1H, bd, J = 15.1 Hz, H-14b), 1.97 (3H, d, J = 1.3 Hz, H-27), 1.87 (1H, m, H-11b), 1.73 (1H, m, H-8), 1.67 (1H, m, H-10a), 1.65 (3H, bs, H-26), 1.32 (3H, s, H-23), 1.26 (2H, m, H-9), 1.24 (1H, m, H-10b), 1.18 (3H, d, J = 6.9 Hz, H-24), 1.07 (3H, s, H-22), 1.00 (3H, d, J = 7.0 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.6 (s, C-5), 170.3 (s, C-1), 161.0 (s, C-20), 138.6 (s, C-12), 138.4 (s, C-16), 137.5 (s, C-18), 135.6 (d, C-19), 120.8 (d, C-13), 115.8 (d, C-17), 78.9 (d, C-15), 74.3 (d, C-7), 72.7 (d, C-3), 53.3 (s, C-4), 42.0 (d, C-6), 39.6 (t, C-2), 38.6 (d, C-8), 32.4 (t, C-14), 31.9 (t, C-9), 31.6 (t, C-11), 25.6 (t, C-10), 23.0 (q, C-26), 22.8 (q, C-23), 18.8 (q, C-22), 16.1 (q, C-27), 15.9 (q, C-25), 13.8 (q, C-21), 13.6 (q, C-24); EIMS *m/z* 475 $[M]^+$ (11), 288 (9), 287 (5), 188(7), 171 (32), 152 (100),

111 (10); HREIMS *m/z* 475.2913 (calcd. for $C_{27}H_{41}NO_6$, 475.2934).

Epothilone C_1 (16): colorless amorphous solid; $[\alpha]^{22}_D$ −114.0 (*c* 10.0, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (16500), 248 (12500); IR (KBr) ν_{max} 3440, 2933, 2877, 2858, 1730, 1708, 1457, 1244, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.96 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.47 (1H, dd, *J* = 9.2, 3.0 Hz, H-15), 5.43 (1H, m, H-12), 5.40 (1H, m, H-13), 4.40 (1H, ddd, *J* = 6.2, 6.1, 6.1 Hz, H-3), 3.69 (1H, dd, *J* = 5.7, 3.6 Hz, H-7), 3.01 (1H, dq, *J* = 5.7, 6.9 Hz, H-6), 3.01 (1H, bs, 3-OH), 2.84 (1H, dq, *J* = 5.2, 7.0 Hz, H-4), 2.68 (3H, s, H-21), 2.66 (1H, ddd, *J* = 16.4, 9.2, 7.3 Hz, H-14a), 2.64 (1H, dd, *J* = 15.9, 7.1 Hz, H-2a), 2.54 (1H, dd, *J* = 15.9, 6.1 Hz, H-2b), 2.38 (1H, bd, *J* = 16.4 Hz, H-14b), 2.35 (1H, bs, 7-OH), 2.07 (3H, bs, H-27), 2.03 (2H, m, H-11), 1.62 (1H, m, H-10a), 1.53 (1H, m, H-8), 1.35 (1H, m, H-9a), 1.22 (1H, m, H-9b), 1.19 (3H, d, *J* = 6.9 Hz, H-24), 1.14 (3H, d, *J* = 6.9 Hz, H-23), 1.10 (1H, m, H-10b), 0.95 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (5), 324 (8), 290 (8), 204 (7), 168 (100), 164 (15), 139 (36); HREIMS *m/z* 463.2381 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone D_1 (17): colorless amorphous solid; $[\alpha]^{22}_D$ −118.6 (*c* 0.5, MeOH); UV (MeOH) λ_{max} nm (ε) 208 (18300), 249 (11900); IR (KBr) ν_{max} 3439, 2965, 2934, 2877, 1729, 1707, 1456, 1250, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.51 (1H, dd, *J* = 9.5, 3.4 Hz, H-15), 5.16 (1H, dd, *J* = 8.0, 4.2 Hz, H-13), 4.42 (1H, ddd, *J* = 7.1, 6.3, 5.5 Hz, H-3), 3.70 (1H, dd, *J* = 6.5, 2.9 Hz, H-7), 3.07 (1H, dq, *J* = 6.5, 6.9 Hz, H-6), 2.95 (1H, dq, *J* = 4.7, 7.0 Hz, H-4), 2.71 (3H, s, H-21), 2.69 (1H, dd, *J* = 16.0, 6.3 Hz, H-2a), 2.64 (1H, m, H-14a), 2.59 (1H, dd, *J* = 16.0, 7.1 Hz, H-2b), 2.46 (1H, bs, 3-OH), 2.38 (1H, bd, *J* = 16.0 Hz, H-14b), 2.19 (1H, ddd, *J* = 13.3, 8.6, 5.7 Hz, H-11a), 2.10 (3H, d, *J* = 1.4 Hz, H-27), 2.02 (1H, bs, 7-OH), 1.91 (1H, ddd, *J* = 13.3, 6.0, 6.0 Hz, H-11b), 1.68 (1H, m, H-10a), 1.66 (3H, bs, H-26), 1.53 (1H, m, H-8), 1.37 (1H, m, H-9a), 1.26 (1H, m, H-9b), 1.24 (3H, d, *J* = 6.9 Hz, H-24), 1.19 (1H, m, H-10b), 1.14 (3H, d. *J* = 7.0, H-23), 0.99 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.0 (s, C-5), 169.7 (s, C-1), 165.0 (s, C-20), 152.2 (s, C-18), 138.5 (s, C-12), 137.7 (s, C-16), 120.7 (d, C-13), 120.1 (d, C-17), 116.3 (d, C-19), 78.8 (d, C-15), 77.2 (d, C-7), 67.7 (d, C-3), 52.1 (d, C-4), 46.5 (d, C-6), 40.6 (t, C-2), 37.6 (d, C-8), 32.3 (t, C-14), 31.8 (t, C-11), 29.5(t, C-9), 25.5 (t, C-10), 23.1 (q, C-26), 19.2 (q, C-21), 15.5 (q, C-27), 16.6 (q, C-25), 14.5 (q, C-24), 9.7 (q, C-23); EIMS *m/z* 477 $[M]^+$ (13), 304 (19), 303 (31), 218 (40), 204 (41), 168 (100), 164 (45), 157 (25), 139 (18); HREIMS *m/z* 477.2544 (calcd. for $C_{26}H_{39}NO_5S$, 477.2549).

Epothilone C_2 (18): colorless amorphous solid; $[\alpha]^{22}_D$ −11.6 (*c* 10.0, MeOH); UV (MeOH) λ_{max} nm (ε) 212 (15500), 249 (12100); IR (KBr) ν_{max} 3428, 2962, 2929, 2877, 2859, 1734, 1705, 1460, 1253, 982 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.99 (1H, s, H-19), 6.66 (1H,

bs, H-17), 5.55 (1H, ddd, J = 10.4, 9.2, 6.1 Hz, H-12), 5.38 (1H, ddd, J = 10.4, 9.3, 6.2 Hz, H-13), 5.22 (1H, dd, J = 8.8, 2.8 Hz, H-15), 4.42 (1H, dddd, J = 9.4, 5.6, 4.2, 4.1 Hz, H-3), 3.93 (1H, d, J = 5.6 Hz, 3-OH), 3.86 (1H, m, H-7), 3.15 (1H, bs, 7-OH), 3.12 (1H, dq, J = 4.2, 7.0 Hz, H-4), 3.00 (1H, dq, J = 6.9, 7.0 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dddd, J = 15.1, 9.3, 8.8, 0.8 Hz, H-14a), 2.58 (1H, dd, J = 15.4, 9.4 Hz, H-2a), 2.38 (1H, dd, J = 15.4, 4.1 Hz, H-2b), 2.31 (1H, ddd, J = 15.1, 6.2, 2.8 Hz, H-14b), 2.08 (3H, d, J = 1.3 Hz, H-27), 2.15 (1H, m, H-11a), 2.04 (1H, m, H-11b), 1.71 (1H, m, H-8), 1.59 (1H, m, H-10a), 1.43 (1H, m, H-9a), 1.31 (1H, m, H-9b), 1.26 (3H, d, J = 7.0 Hz, H-24), 1.15 (3H, d, J = 7.0 Hz, H-23), 1.11 (1H, m, H-10b), 1.00 (3H, d, J = 6.9 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (7), 324 (7), 306 (8), 290 (17), 168 (100), 164 (14), 139 (27); HREIMS *m/z* 463.2392 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone D_2 (19): colorless amorphous solid; $[\alpha]^{22}_D$ −12.5 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (15400), 248 (11200); IR (KBr) ν_{max} 3436, 2965, 2930, 2877, 1732, 1705, 1458, 1253, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.18 (1H, dd, J = 7.9, 4.9 Hz, H-15), 5.18 (1H, ddd, J = 9.6, 5.4, 1.0 Hz, H-13), 4.27 (1H, m, H-3), 3.88 (1H, dd, J = 5.6, 4.6 Hz, H-7), 3.19 (1H, bs, 3-OH), 3.07 (1H, dq, J = 4.3, 7.0 Hz, H-4), 2.95 (1H, dq, J = 5.6, 7.0 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dd, J = 14.9, 7.8 Hz, H-2a), 2.56 (1H, ddd, J = 14.7, 9.6, 7.9 Hz, H-14a), 2.43 (1H, dd, J = 14.9, 5.6 Hz, H-2b), 2.38 (1H, bs, 7-OH), 2.26 (1H, ddd, J = 14.5, 5.4, 4.9 Hz, H-14b), 2.19 (1H, ddd, J = 13.0, 10.4, 5.4 Hz, H-11a), 2.10 (3H, d, J = 1.4 Hz, H-27), 1.95 (1H, ddd, J = 13.0, 10.3, 5.3 Hz, H-11b), 1.72 (1H, m, H-8), 1.68 (3H, bs, H-26), 1.61 (1H, m, H-10a), 1.39 (2H, m, H-9), 1.21 (1H, m, H-10b),

1.19 (3H, d, J = 6.9 Hz, H-24), 1.17 (3H, d. J = 7.0, H-22), 1.00 (3H, d, J = 6.9 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.8 (s, C-5), 170.4 (s, C-1), 164.9 (s, C-20), 152.3 (s, C-18), 139.8 (s, C-12), 137.5 (s, C-16), 120.5 (d, C-17), 119.2 (d, C-13), 116.3 (d, C-19), 80.0 (d, C-15), 74.3 (d, C-7), 69.7 (d, C-3), 48.6 (d, C-4), 48.4 (d, C-6), 39.9 (t, C-2), 36.6 (d, C-8), 32.2 (t, C-14), 32.7 (t, C-11), 30.9 (t, C-9), 26.0 (t, C-10), 23.6 (q, C-26), 19.2 (q, C-21), 15.4 (q, C-27), 17.1 (q, C-25), 12.4 (q, C-24),12.7 (q, C-23); EIMS *m/z* 477 $[M]^+$ (22), 304 (19), 303 (17), 218 (22), 204 (25), 168 (100), 164 (28), 157 (31), 139 (21); HREIMS *m/z* 477.2545 (calcd. for $C_{26}H_{39}NO_5S$, 477.2549).

Epothilone C_3 (20): colorless amorphous solid; $[\alpha]^{22}_D$ –62.1 (*c* 5.0, MeOH); UV (MeOH) λ_{max} nm (ε) 212 (16200), 248 (12300); IR (KBr) ν_{max} 3432, 2928, 2878, 2858, 1736, 1698, 1252, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.44 (1H, ddd, J = 10.9, 10.3, 5.4 Hz, H-12), 5.33 (1H, ddd, J = 10.9, 9.3, 4.6 Hz, H-13), 5.23 (1H, dd, J = 9.5, 2.2 Hz, H-15), 4.36 (1H, ddd, J = 11.3, 5.6, 2.3 Hz, H-3), 4.04 (1H, d, J = 5.6 Hz, 3-OH), 3.93 (1H, ddd, J = 9.5, 2.3, 1.4 Hz, H-7), 3.56 (1H, bd, J = 2.3 Hz, 7-OH), 2.70 (1H, dd, J = 18.0, 1.4 Hz, H-6a), 2.67 (3H, s, H-21), 2.61 (1H, ddd, J = 15.3, 9.5, 9.3 Hz, H-14a), 2.38 (1H, dd, J = 14.3, 11.3 Hz, H-2a), 2.36 (1H, dd, J = 18.0, 9.5 Hz, H-6b), 2.28 (1H, bd, J = 15.3 Hz, H-14b), 2.12 (1H, m, H-11a), 2.06 (1H, dd, J = 14.3, 2.3 Hz, H-2b), 2.03 (3H, d, J = 1.3 Hz, H-27), 1.96 (1H, m, H-11b), 1.75 (1H, m, H-8), 1.54 (1H, m, H-10a),1.26 (1H, m, H-9a), 1.25 (3H, s, H-23), 1.17 (1H, m, H-10b), 1.15 (1H, m, H-9b), 1.03 (3H, s, H-22), 0.91 (3H, d, J = 6.8 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (28), 290 (14), 168 (100), 164 (36), 157 (44), 151 (25); HREIMS *m/z* 463.2379 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone C_4 (21): colorless amorphous solid; $[\alpha]^{22}_D$ –75.6 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 212 (17200), 248 (12500); IR (KBr) ν_{max} 3434, 2974, 2932, 2859, 1735, 1686, 1252, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.96 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.43 (1H, m, H-12), 5.40 (1H, m, H-13), 5.26 (1H, dd, *J* = 9.6, 2.3 Hz, H-15), 4.41 (1H, ddd, *J* = 11.4, 5.8, 2.5 Hz, H-3), 3.78 (1H, m, H-7), 3.70 (1H, bs, 3-OH), 3.46 (1H, d, *J* = 0.9 Hz, 7-OH), 3.01 (1H, dq, *J* = 0.5, 7.0 Hz, H-6), 2.69 (3H, s, H-21), 2.66 (1H, ddd, *J* = 15.3, 9.6, 8.8 Hz, H-14a), 2.47 (1H, dd, *J* = 14.5, 11.4 Hz, H-2a), 2.29 (1H, m, H-14b), 2.25 (1H, dd, *J* = 14.5, 2.5 Hz, H-2b), 2.24 (1H, m, H-11a), 2.07 (3H, d, *J* = 1.4 Hz, H-27), 1.96 (1H, m, H-11b), 1.51 (2H, m, H-8), 1.44 (2H, m, H-10),1.37 (2H, m, H-9), 1.32 (3H, s, H-23), 1.17 (3H, d, *J* = 7.0 Hz, H-24), 1.07 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (7), 276 (15), 171 (33), 168 (100), 164 (23), 151 (22), 111 (13); HREIMS *m/z* 463.2373 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone C_5 (22): colorless amorphous solid; $[\alpha]^{22}_D$ –158.2 (*c* 0.5, MeOH); UV (MeOH) λ_{max} nm (ε) 205 (19500), 247 (12700); IR (KBr) ν_{max} 3447, 2972, 2927, 1737, 1690, 1450, 1252, 1181, 986 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.93 (1H, s, H-19), 6.48 (1H, bs, H-17), 5.48 (1H, ddd, *J* = 10.7, 6.2, 6.2 Hz, H-12), 5.39 (1H, m, H-13), 5.37 (1H, m, H-9), 5.34 (1H, dd, *J* = 8.0, 2.3 Hz, H-15), 4.29 (1H, dd, *J* = 6.0, 2.6 Hz, H-7), 4.09 (1H, ddd, *J* = 10.8, 7.1, 2.9 Hz, H-3), 3.59 (1H, d, *J* = 7.1 Hz, 3-OH), 3.17 (1H, dq, *J* = 6.0, 6.9 Hz, H-6), 2.68 (3H, s, H-21), 2.54 (1H, ddd, *J* = 15.2, 8.1, 8.0 Hz, H-14a), 2.44 (1H, bs, 7-OH), 2.42 (1H, dd, *J* = 15.1, 2.9 Hz, H-2a), 2.41 (1H, ddd, *J* = 15.2, 2.3, 2.3 Hz, H-14b), 2.34 (1H, dd, *J* = 15.1, 10.8 Hz, H-2b), 2.20 (1H, m, H-10a), 2.18 (2H, m, H-11), 2.12 (1H, m, H-10b), 2.06 (3H, bs, H-27), 1.67 (3H, bs, H-25), 1.27 (3H, s, H-23), 1.21 (3H, d, *J* = 6.9 Hz, H-24), 1.15 (3H, s, H-22); ^{13}C NMR,

see Table 1; EIMS *m/z* 475 $[M]^+$ (6), 392 (7), 304 (6), 288 (33), 204 (76), 171 (19), 168 (100), 164 (12); HREIMS *m/z* 475.2380 (calcd. for $C_{26}H_{37}NO_5S$, 475.2392).

Epothilone D_5 (23): colorless amorphous solid; $[\alpha]^{22}_D$ –150 (*c* 0.2, MeOH); UV (MeOH) λ_{max} nm (ε) 205 (23300), 248 (13600); IR (KBr) ν_{max} 3439, 2967, 2927, 1736, 1690, 1451, 1254, 1181, 987 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ; 6.94 (1H, s, H-19), 6.51 (1H, bs, H-17), 5.34 (1H, bs, H-9), 5.29 (1H, dd, *J* = 8.0, 2.4 Hz, H-15), 5.16 (1H, dd, *J* = 8.2, 6.2 Hz, H-13), 4.30 (1H, bd, *J* = 4.9 Hz, H-7), 4.19 (1H, ddd, *J* = 10.8, 7.6, 3.0 Hz, H-3), 3.68 (1H, d, *J* = 7.6 Hz, 3-OH), 3.17 (1H, dq, *J* = 4.9, 7.0 Hz, H-6), 2.69 (3H, s, H-21), 2.65 (1H, d, *J* = 2.1 Hz, 7-OH), 2.56 (1H, ddd, *J* = 16.2, 8.2, 8.0 Hz, H-14a), 2.40 (1H, dd, *J* = 15.0, 3.0 Hz, H-2a), 2.39 (1H, bd, *J* = 16.2 Hz, H-14b), 2.34 (1H, dd, *J* = 15.0, 10.8 Hz, H-2b), 2.25 (2H, m, H-10a and H-11a), 2.20 (1H, m, H-10b), 2.17 (1H, m, H-11b), 2.05 (3H, d, *J* = 1.0 Hz, H-27), 1.69 (3H, bs, H-25), 1.68 (3H, bs, H-26), 1.29 (3H, s, H-23), 1.23 (3H, d, *J* = 7.0 Hz, H-24), 1.16 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS *m/z* 489 $[M]^+$ (4), 406 (4), 338 (7), 302 (13), 218 (35), 171 (10), 168 (100), 153 (20), 125 (10); HREIMS *m/z* 489.2536 (calcd. for $C_{27}H_{39}NO_5S$, 489.2549).

Epothilone C_6 (24): colorless amorphous solid; $[\alpha]^{22}_D$ –205.2 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 218 (24600), 237 (28800); IR (KBr) ν_{max} 3435, 2967, 2927, 2882, 1732, 1688, 1465, 1258, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.97 (1H, s, H-19), 6.58 (1H, bs, H-17), 6.43 (1H, dd, 15.5, 10.8 Hz, H-11), 6.11 (1H, dd, *J* = 10.8, 10.6 Hz, H-12), 5.75 (1H, ddd, *J* = 15.5, 8.3, 5.6 Hz, H-10), 5.34 (1H, m, H-13), 5.34 (1H, dd, *J* = 9.7, 2.4 Hz, H-15), 4.16 (1H, ddd, *J* = 9.2, 4.9, 4.3 Hz, H-3), 3.74 (1H, ddd, *J* = 2.2, 2.1, 1.7 Hz, H-7), 3.24 (1H, dq, *J* = 2.1, 6.9 Hz, H-6), 3.06 (1H, d, *J* = 2.2 Hz, 7-OH), 2.93 (1H, d, *J* = 4.9 Hz, 3-OH), 2.78 (1H, dddd,

J = 14.1, 9.9 9.7, 0.7, H-14a), 2.71 (3H, s, H-21), 2.48 (1H, m, H-9a), 2.47 (1H, dd, J = 15.5, 9.2 Hz, H-2a), 2.40 (1H, dd, J = 15.5, 4.3 Hz, H-2b), 2.38 (1H, bdd, J = 14.1, 7.8 Hz, H-14b), 2.11 (3H, d, J = 1.3 Hz, H-27), 1.96 (1H, m, H-8), 1.33 (3H, s, H-23), 1.11 (3H, d, J = 6.9 Hz, H-24), 1.06 (3H, s, H-22), 1.05 (3H, d, J = 6.8 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 475 $[M]^+$ (13), 387 (2), 316 (4), 288 (15), 230 (16), 204 (9), 171 (18), 168 (100), 164 (14), 151 (17); HREIMS *m/z* 475.2361 (calcd. for $C_{26}H_{37}NO_5S$, 475.2392).

Epothilone C_7 (25): colorless amorphous solid; $[\alpha]_D^{22}$ **–XXX (*c* 2.0, MeOH); UV** (MeOH) λ_{max} **nm** (ε) XXX (XXX), XXX (XXX); **IR (KBr)** ν_{max} **XXX cm^{-1}**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (1H, s, H-19), 6.66 (1H, bs, H-17), 5.59 (1H, ddd, J = 11.1, 11.1, 3.8 Hz, H-12), 5.40 (1H, dd, J = 11.1, 9.2, H-13), 5.03 (1H, d, J = 9.3 Hz, H-15), 4.62 (1H, dd, J = 9.3, 9.2 Hz, H-14), 4.18 (1H, bd, J = 11.0 Hz, H-3), 3.72 (1H, bs, H-7), 3.20 (1H, bs, 3-OH), 3.09 (1H, dq, J = 1.9, 6.8 Hz, H-6), 3.00 (1H, bs, 7-OH), 2.69 (3H, s, H-21), 2.47 (1H, dd, J = 14.8, 11.0 Hz, H-2a), 2.32 (1H, dd, J = 14.8, 2.6 Hz, H-2b), 2.27 (1H, m, H-11a), 2.19 (3H, bs, H-27), 2.13 (1H, m, H-11b), 1.76 (1H, m, H-8), 1.70 (1H, m, H-10a), 1.35 (1H, m, H-9a), 1.32 (3H, s, H-23), 1.23 (1H, m, H-9b), 1.21 (1H, m, H-10b), 1.18 (3H, d, J = 6.8 Hz, H-24), 1.08 (3H, s, H-22), 1.00 (3H, d, J = 6.9 Hz, H-25); **EIMS *m/z* 493 $[M]^+$ XXX; HREIMS *m/z* 493.XXX (calcd. for $C_{26}H_{39}NO_6S$, 493.2498).**

Epothilone C_8 (26): colorless amorphous solid; $[\alpha]^{22}_D$ –75.2 (*c* 2.5, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (16800), 248 (17800); IR (KBr) ν_{max} 3443, 2932, 2881, 1734, 1689, 1465, 1255, 1183, 976 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (1H, s, H-19), 6.62 (1H, dd, J = 15.6, 0.6 Hz, H-17), 6.49 (1H, dd, J = 15.6, 6.6 Hz, H-16), 5.52 (1H, dddd, J = 9.5, 6.6, 2.8, 0.6 Hz, H-

15), 5.42 (1H, m, H-12), 5.41 (1H, m, H-13), 4.13 (1H, ddd, J = 11.0, 5.3, 2.8 Hz, H-3), 3.69 (1H, ddd, J = 3.7, 2.8, 2.5 Hz, H-7), 3.11 (1H, dq, J = 2.5, 6.8 Hz, H-6), 2.95 (1H, d, J = 5.3 Hz, 3-OH), 2.90 (1H, d, J = 2.8 Hz, 7-OH), 2.69 (3H, s, H-21), 2.67 (1H, ddd, J = 14.9, 9.5, 8.4 Hz, H-14a), 2.48 (1H, dd, J = 15.6, 11.0 Hz, H-2a), 2.33 (1H, dd, J = 15.6, 2.8 Hz, H-2b), 2.30 (1H, bd, J = 14.9 Hz, H-14b), 2.14 (1H, m, H-11a), 2.03 (1H, m, H-11b), 1.71 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.31 (1H, m, H-9a), 1.29 (3H, s, H-23), 1.17 (3H, d, J = 6.8 Hz, H-24), 1.16 (1H, m, H-10b), 1.14 (1H, m, H-9b), 1.05 (3H, s, H-22), 0.97 (3H, d, J = 7.1 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (21), 310 (10), 276 (21), 171 (83), 154 (100), 150 (27), 111 (18); HREIMS *m/z* 463.2382 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone C_9 (27): colorless amorphous solid; $[\alpha]^{22}_D$ –93.4 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 209 (15200), 254 (15700); IR (KBr) ν_{max} 3416, 2966, 2932, 1736, 1689, 1463, 1249, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (1H, s, H-19), 6.65 (1H, bs, H-17), 6.56 (1H, dd, J = 10.6, 4.4 Hz, 27-OH), 5.55 (1H, d, J = 6.2 Hz, 3-OH),5.52 (1H, dd, J = 11.6, 2.0 Hz, H-15), 5.44 (1H, dddd, J = 11.2, 10.7, 3.1, 1.7 Hz, H-12), 5.35 (1H, dddd, J = 11.0, 10.7, 3.9, 1.7 Hz, H-13), 4.47 (1H, ddd, J = 12.5, 4.4, 1.3 Hz, H-27a), 4.35 (1H, ddd, J = 11.7, 6.2, 2.6 Hz, H-3), 4.20 (1H, ddd, J = 12.5, 10.6, 0.9 Hz, H-27b), 3.63 (1H, ddd, J = 4.6, 1.8, 0.9 Hz, H-7), 3.24 (1H, d, J = 1.8 Hz, 7-OH), 3.13 (1H, dq, J = 0.9, 6.8 Hz, H-6), 2.80 (1H, ddd, J = 14.8, 11.6, 11.0 Hz, H-14a), 2.71 (3H, s, H-21), 2.40 (1H, dd, J = 14.4, 11.7 Hz, H-2a), 2.24 (1H, m, H-11a), 2.06 (1H, dd, J = 14.4, 2.6 Hz, H-2b), 2.01 (1H, ddd, J = 14.8, 3.9, 2.0 Hz, H-14b), 2.00 (1H, m, H-11b), 1.77 (1H, m, H-8), 1.69 (1H, m, H-10a), 1.35 (1H, m, H-9a), 1.35 (3H, s, H-23), 1.19 (1H, m, H-10b), 1.19 (3H, d, J = 6.8 Hz, H-24), 1.18 (1H, m, H-9b), 1.01 (3H, d, J =

7.1 Hz, H-25), 0.98 (3H, s, H-22); ^{13}C NMR, see Table 1; EIMS *m/z* 493 $[M]^+$ (17), 306 (64), 184 (50), 171 (30), 167 (38), 166 (100), 138 (12); HREIMS *m/z* 493.2502 (calcd. for $C_{26}H_{39}NO_6S$, 493.2498).

trans-Epothilone C_1 (28): colorless amorphous solid; $[\alpha]^{22}_D$ −84 (*c* 0.2, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (17400), 248 (12900); IR (KBr) ν_{max} 3433, 2961, 2933, 2879, 1730, 1708, 1457, 1251, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.00 (1H, s, H-19), 6.64 (1H, bs, H-17), 5.45 (1H, ddd, *J* = 15.2, 6.5, 6.5 Hz, H-12), 5.42 (1H, dd, *J* = 6.4, 3.7 Hz, H-15), 5.35 (1H, dt, *J* = 15.2, 7.1 Hz, H-13), 4.42 (1H, m, H-3), 3.58 (1H, ddd, *J* = 8.1, 7.9, 2.8 Hz, H-7), 3.24 (1H, m, H-6), 3.14 (1H, dq, *J* = 4.0, 6.9 Hz, H-6), 2.92 (1H, d, *J* = 7.9 Hz, 7-OH), 2.71 (3H, s, H-21), 2.71 (2H, m, H-2), 2.53 (2H, m, H-14), 2.17 (1H, d, *J* = 2.17 Hz, 3-OH), 2.11 (1H, m, H-11a), 2.06 (3H, bs, H-27), 1.93 (1H, m, H-11b), 1.68 (1H, m, H-9a), 1.65 (1H, m, H-10a), 1.33 (1H, m, H-8), 1.26 (3H, d, *J* = 6.8 Hz, H-24), 1.16 (1H, m, H-10b), 1.12 (3H, d, *J* = 6.9 Hz, H-22), 1.07 (1H, m, H-9b), 1.00 (3H, d, *J* = 6.8 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (6), 290 (21), 289 (20), 204 (23), 194 (19), 190 (22), 168 (100), 164 (48), 157 (14), 152 (19), 151 (17), 139 (15), 111 (18); HREIMS *m/z* 463.2371 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

trans-Epothilone C_2 (29): colorless amorphous solid; $[\alpha]^{22}_D$ −3 (*c* 1.5, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (15800), 248 (11900); IR (KBr) ν_{max} 3435, 2963, 2931, 2878, 1731, 1706, 1457, 1273, 979 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.99 (1H, s, H-19), 6.57 (1H, bs, H-17), 5.56 (1H, ddd, *J* = 15.1, 7.4, 7.0 Hz, H-12), 5.41 (1H, ddd, *J* = 15.1, 7.0, 6.9 Hz, H-13), 5.41 (1H, dd, *J* = 7.7, 2.8 Hz, H-15), 4.13 (1H, dddd, *J* = 6.7, 6.2, 5.6, 5.1 Hz, H-3), 3.78 (1H, ddd, *J* = 8.2, 6.5, 1.9 Hz, H-7), 3.18 (1H, d, *J* = 5.6 Hz, 3-OH), 3.06 (1H, dq, *J* = 8.2, 7.1 Hz,

H-6), 2.98 (1H, dq, J = 6.2, 7.0 Hz, H-4), 2.71 (3H, s, H-21), 2.64 (1H, dd, J = 15.1, 6.7 Hz, H-2a), 2.54 (1H, dd, J = 15.1, 5.1 Hz, H-2b), 2.44 (2H, m, H-14), 2.22 (1H, dddd, J = 13.8, 7.0, 6.2, 2.9 Hz, H-11a), 2.10 (3H, d, J = 1.1 Hz, H-27), 2.09 (1H, d, J = 6.5 Hz, 7-OH), 1.88 (1H, dddd, J = 13.8, 10.9, 7.4, 2.9 Hz, H-11b), 1.65 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.56 (1H, dddd, J = 12.7, 12.7, 3.9, 3.9 Hz, H-9a), 1.20 (3H, d, J = 7.1 Hz, H-24), 1.15 (3H, d, J = 7.0 Hz, H-23), 1.13 (1H, m, H-10b), 1.04 (1H, m, H-9b), 1.01 (3H, d, J = 7.0 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (13), 290 (11), 190 (10), 168 (100), 164 (20), 157 (26), 139 (17); HREIMS *m/z* 463.2383 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone I_1 (30): colorless amorphous solid; $[\alpha]_D^{22}$ **–XXX (*c* XXX, MeOH); UV** (MeOH) λ_{max} **nm** (ε) **XXX; IR** (KBr) ν_{max} **XXX cm^{-1}**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (1H, s, H-19), 6.54 (1H, bs, H-17), 5.49 (1H, ddd, J = 10.3, 7.3, 7.3 Hz, H-12), 5.33 (1H, dd, J = 8.3, 4.4 Hz, H-15), 5.31 (1H, m, H-13), 4.15 (1H, ddd, J = 8.0, 5.0, 4.6 Hz, H-3), 3.80 (1H, m, H-7), 3.21 (1H, dq, J = 6.0, 6.9 Hz, H-6), 2.89 (1H, d, J = 5.0 Hz, 3-OH); 2.70 (3H, s, H-21), 2.65 (1H, ddd, J = 15.8, 8.5, 8.3 Hz, H-14a), 2.42 (2H, m, H-2), 2.35 (1H, m, H-14b), 2.27 (1H, bd, J = 3.3 Hz, 7-OH), 2.13 (1H, m, H-11a), 2.09 (3H, d, J = 1.2 Hz, H-27), 2.00 (1H, m, H-11b), 1.72 (1H, m, H-8), 1.40 (2H, m, H-10$_\beta$), 1.37 (1H, m, H-9$_\beta$a), 1.36 (2H, m, H-9$_\alpha$), 1.32 (3H, s, H-23), 1.27 (3H, m, H-9$_\beta$b and H-10$_\alpha$), 1.13 (3H, d, J = 6.9 Hz, H-24), 1.09 (3H, s, H-22), 0.94 (3H, d, J = 6.9 Hz, H-25); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 221.3 (s, C-5), 171.1 (s, C-1), 164.8 (s, C-20), 152.4 (s, C-18), 137.4 (s, C-16), 133.8 (d, C-12), 124.6 (d, C-13), 120.0 (d, C-17), 116.2 (d, C-19), 78.8 (d, C-15), 74.9 (d, C-7), 74.7 (d, C-3), 51.6 (s, C-4), 43.7 (d, C-6), 38.9 (t, C-2), 34.3 (d, C-8), 31.6 (t, C-14), 29.3 (t, C-9$_\alpha$), 28.6 (t, C-10$_\beta$), 28.2 (t, C-10$_\alpha$), 26.6 (t, C-

11), 24.8 (t, C-9$_\beta$), 23.6 (q, C-22), 19.3 (q, C23), 19.3 (q, C-21), 16.5 (q, C-25), 15.5 (q, C-27), 13.7 (q, C-24); EIMS *m/z* 505 $[M]^+$ XXX; HREIMS *m/z* 505.XXX (calcd. for $C_{28}H_{43}NO_5S$, 505.XXX).

Epothilone I_2 (31): colorless amorphous solid; $[\alpha]_D^{22}$ –XXX (*c* XXX, MeOH); UV (MeOH) λ_{max} nm (ε) XXX; IR (KBr) ν_{max} XXX cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (1H, s, H-19), 6.53 (1H, bs, H-17), 5.40 (1H, m, H-12), 5.38 (1H, dd, *J* = 9.8, 3.3 Hz, H-15), 5.37 (1H, m, H-13), 4.21 (1H, ddd, *J* = 8.6, 3.8, 3.6 Hz, H-3), 3.85 (1H, ddd, *J* = 8.5, 5.8, 2.2 Hz, H-7), 3.18 (1H, dq, *J* = 8.5, 7.0 Hz, H-6), 2.70 (3H, s, H-21), 2.65 (1H, ddd, *J* = 15.2, 9.8, 9.0 Hz, H-14a), 2.51 (1H, d, *J* = 3.6 Hz, 3-OH), 2.37 (2H, m, H-2), 2.32 (1H, bd, *J* = 15.2 Hz, H-14b), 2.09 (3H, d, *J* = 1.3 Hz, H-27), 2.07 (2H, m, H-11), 1.78 (1H, m, H-8), 1.65 (1H, d, *J* = 5.8 Hz, 7-OH), 1.57 (1H, m, H-10$_\beta$a), 1.44 (1H, m, H-10$_\alpha$a), 1.42 (1H, m, H-9$_\beta$), 1.32 (3H, s, H-23), 1.21 (1H, m, H-10$_\beta$b), 1.17 (3H, d, *J* = 7.0 Hz, H-24), 1.13 (2H, m, H-9$_\alpha$), 1.06 (3H, s, H-22), 0.95 (3H, d, *J* = 7.0 Hz, H-25$_\alpha$), 0.91 (3H, d, *J* = 6.5 Hz, H-25$_\beta$), 0.68 (1H, m, H-10$_\alpha$b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.4 (s, C-5), 171.3 (s, C-1), XXX (s, C-20), 152.4 (s, C-18), 137.6 (s, C-16), 134.5 (d, C-12), 125.3 (d, C-13), 119.6 (d, C-17), 116.2 (d, C-19), 78.6 (d, C-15), 77.2 (d, C-7), 75.0 (d, C-3), 51.0 (s, C-4), 44.6 (d, C-6), 38.2 (t, C-2), 36.9 (t, C-9$_\alpha$), 34.5 (t, C-10$_\alpha$), 32.6 (d, C-8), 32.0 (t, C-14), 30.0 (d, C-9$_\beta$), 27.4 (t, C-11), 26.6 (t, C-10$_\beta$), 25.0 (q, C-22), 21.5 (q, C-25$_\beta$), 19.3 (q, C-21), 17.9 (q, C-25$_\alpha$), 17.7 (q, C-23), 15.8 (q, C-24), 15.6 (q, C-27); EIMS *m/z* 519 $[M]^+$ XXX; HREIMS *m/z* 519.XXX (calcd. for $C_{29}H_{45}NO_5S$, 519.XXX).

Epothilone I_3 (32): colorless amorphous solid; $[\alpha]_D^{22}$ –XXX (*c* XXX, MeOH); UV (MeOH) λ_{max} nm (ε) XXX; IR (KBr) ν_{max} XXX cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.95 (1H,

s, H-19), 6.52 (1H, bs, H-17), 5.32 (1H, dd, J = 9.1, 3.0 Hz, H-15), 5.08 (1H, dd, J = 8.5, 3.9 Hz, H-13), 4.13 (1H, ddd, J = 9.4, 4.3, 3.2 Hz, H-3), 3.81 (1H, m, H-7), 3.18 (1H, dq, J = 6.8, 7.0 Hz, H-6), 2.83 (1H, d, J = 4.3 Hz, 3-OH), 2.70 (3H, s, H-21), 2.61 (1H, ddd, J = 15.8, 9.1, 8.5 Hz, H-14a), 2.43 (1H, dd, J = 14.0, 3.2 Hz, H-2a), 2.38 (2H, dd, J = 14.0, 9.4 Hz, H-2b), 2.30 (1H, bd, J = 15.8 Hz, H-14b), 2.16 (1H, ddd, J = 14.1, 8.3, 7.4 Hz, H-11a), 2.08 (3H, d, J = 1.0 Hz, H-27), 1.99 (1H, d, J = 4.7 Hz, 7-OH), 1.92 (1H, ddd, J = 14.1, 6.3, 6.3 Hz, H-11b), 1.82 (1H, m, H-8), 1.67 (3H, s, H-26), 1.51 (1H, m, H-10$_\beta$a), 1.40 (1H, m, H-9$_\beta$), 1.33 (1H, m, H-10$_\beta$b), 1.31 (3H, s, H-23), 1.27 (1H, m, H-10$_\alpha$a), 1.23 (1H, m, H-9$_\alpha$a), 1.16 (3H, d, J = 7.0 Hz, H-24), 1.10 (1H, m, H-9$_\alpha$b), 1.07 (3H, s, H-22), 0.95 (3H, d, J = 7.0 Hz,H-25$_\alpha$), 0.92 (3H, d, J = 6.5 Hz, H-25$_\beta$), 0.75 (1H, m, H-10$_\alpha$b); **EIMS *m/z* 533 [M]$^+$ XXX; HREIMS *m/z* 533.XXX** (calcd. for $C_{30}H_{47}NO_5S$, 533.XXX).

Epothilone I_4 (33): colorless amorphous solid; $[\alpha]_D^{22}$ –XXX (*c* XXX, MeOH); UV (MeOH) λ_{max} nm (ε) XXX; IR (KBr) ν_{max} XXX cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.95 (1H, s, H-19), 6.53 (1H, bs, H-17), 5.47 (1H, dt, J = 11.1, 5.8 Hz, H-12), 5.33 (1H, ddd, J = 9.2, 3.9, 0.5 Hz, H-15), 5.33 (1H, m, H-13), 4.09 (1H, dddd, J = 9.6, 8.1, 4.5, 3.3 Hz, H-3), 3.83 (1H, m, H-7), 3.57 (1H, bs, 3-OH), 2.89 (1H, dq, J = 7.4, 7.1 Hz, H-6), 2.83 (1H, dq, J = 8.1, 7.1 Hz, H-4), 2.70 (3H, s, H-21), 2.64 (1H, m, H-14a), 2.42 (1H, dd, J = 14.2, 3.3 Hz, H-2a), 2.43 (1H, dd, J = 14.2, 9.6 Hz, H-2b), 2.30 (1H, m, H-14b), 2.10 (3H, d, J = 1.3 Hz, H-27), 2.09 (2H, m, H-11), 1.81 (1H, m, H-8), 1.74 (1H, bd, J = 5.6 Hz, 7-OH), 1.53 (1H, m, H-10$_\beta$a), 1.49 (1H, m, H-9$_\beta$), 1.47 (1H, m, H-10$_\alpha$a), 1.27 (1H, m, H-10$_\beta$b), 1.24 (1H, m, H-9$_\alpha$a), 1.17 (3H, d, J = 7.1 Hz, H-23), 1.14 (1H, m, H-9$_\alpha$b), 1.08 (3H, d, J = 7.1 Hz, H-24), 0.97 (3H, d, J = 6.9 Hz,H-25$_\alpha$),

0.91 (3H, d, J = 6.5 Hz, H-25$_\beta$), 0.79 (1H, m, H-10$_\alpha$b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.0 (s, C-5), 170.8 (s, C-1), 164.8 (s, C-20), 152.4 (s, C-18), 137.1 (s, C-16), 134.6 (d, C-12), 124.7 (d, C-13), 120.2 (d, C-17), 116.4 (d, C-19), 78.7 (d, C-15), 76.4 (d, C-7), 71.3 (d, C-3), 50.7 (d, C-4), 50.1 (d, C-6), 40.7 (t, C-2), 38.5 (t, C-9$_\alpha$), 35.5 (t, C-10$_\alpha$), 33.4 (d, C-8), 31.8 (t, C-14), 30.0 (d, C-9$_\beta$), 27.2 (t, C-11), 26.7 (t, C-10$_\beta$), 21.4 (q, C-25$_\beta$), 19.3 (q, C-21), 18.2 (q, C-25$_\alpha$), 15.4 (q, C-27), 14.4 (q, C-24), 13.1 (q, C-23); **EIMS *m/z* 505 [M]$^+$ XXX; HREIMS *m/z* 505.XXX** (calcd. for $C_{28}H_{43}NO_5S$, 505.XXX).

Epothilone I$_5$ (34): colorless amorphous solid; $[\alpha]_D^{22}$ **–XXX (*c* XXX, MeOH); UV** (MeOH) λ_{max} nm (ε) XXX; IR (KBr) ν_{max} XXX cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (1H, s, H-19), 6.52 (1H, bs, H-17), 5.32 (1H, dd, J = 7.1, 6.2 Hz, H-15), 5.03 (1H, dd, J = 8.4, 5.0 Hz, H-13), 4.05 (1H, dddd, J = 7.5, 7.2, 5.9, 4.6 Hz, H-3), 3.91 (1H, m, H-7), 3.17 (1H, d, J = 5.9 Hz, 3-OH), 2.94 (1H, dq, J = 7.2, 7.1 Hz, H-4), 2.87 (1H, dq, J = 6.5, 6.9 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dd, J = 14.6, 4.6 Hz, H-2a), 2.60 (1H, m, H-14a), 2.53 (1H, dd, J = 14.6, 7.5 Hz, H-2b), 2.31 (1H, m, H-14b), 2.10 (3H, d, J = 1.1 Hz, H-27), 2.10 (1H, m, H-11a), 2.02 (1H, m, H-11b), 1.97 (1H, bd, J = 5.6 Hz, 7-OH), 1.84 (1H, m, H-8), 1.66 (3H, s, H-26), 1.55 (1H, m, H-9$_\beta$), 1.49 (1H, m, H-10$_\beta$a), 1.39 (1H, m, H-10$_\beta$b), 1.33 (1H, m, H-10$_\alpha$a), 1.31 (1H, m, H-9$_\alpha$a), 1.15 (3H, d, J = 7.1 Hz, H-23), 1.12 (1H, m, H-9$_\alpha$b), 1.11 (3H, d, J = 6.9 Hz, H-24), 0.97 (3H, d, J = 6.9 Hz,H-25$_\alpha$), 0.94 (1H, m, H-10$_\alpha$b), 0.93 (3H, d, J = 6.6 Hz, H-25$_\beta$); **EIMS *m/z* 519 [M]$^+$ XXX; HREIMS *m/z* 519.XXX (calcd. for $C_{29}H_{45}NO_5S$, 519.XXX).**

Epothilone I$_\varepsilon$ (35): colorless amorphous solid; $[\alpha]_D^{22}$ **–XXX (*c* XXX, MeOH); UV** (MeOH) λ_{max} nm (ε) XXX; IR (KBr) ν_{max} XXX cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (1H,

s, H-19), 6.52 (1H, bs, H-17), 5.24 (1H, dd, J = 6.9, 6.9 Hz, H-15), 5.02 (1H, dd, J = 8.8, 5.2 Hz, H-13), 4.22 (1H, tdd, J = 6.1, 5.6, 4.8 Hz, H-3), 3.76 (1H, ddd, J = 6.1, 5.7, 5.6 Hz, H-7), 3.13 (1H, d, J = 5.6 Hz, 3-OH), 3.05 (1H, dq, J = 4.8, 7.0 Hz, H-4), 2.79 (1H, dq, J = 5.6, 6.9 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, m, H-14a), 2.57 (2H, d, J = 6.1 Hz, H-2a), 2.30 (1H, m, H-14b), 2.08 (3H, d, J = 1.0 Hz, H-27), 2.02 (2H, m, H-11), 1.73 (1H, d, J = 6.1 Hz, 7-OH), 1.69 (1H, m, H-8), 1.66 (3H, s, H-26), XXX (H-9_α, H-9_β, H-10_α, H-10_β), 1.21 (3H, d, J = 7.0 Hz, H-22), 1.16 (3H, d, J = 6.9 Hz, H-24), 0.94 (3H, d, J = 6.9 Hz,H-25_α), 0.91 (3H, d, J = 6.4 Hz, H-25_β); EIMS *m/z* 519 $[M]^+$ XXX; HREIMS *m/z* 519.XXX (calcd. for $C_{29}H_{45}NO_5S$, 519.XXX).

Epothilone K (36): colorless amorphous solid; $[\alpha]^{22}_D$ –7 (*c* 0.08, MeOH); UV (MeOH) λ_{max} nm (ε) 212 (16700), 248 (12500); IR (KBr) ν_{max} 3431, 2963, 2927, 2856, 1731, 1712, 1262, 1093, 1021, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (1H, s, H-19), 6.51 (1H, bs, H-17), 5.49 (3H, m, H-15, H-13, and H-12), 4.04 (1H, dddd, J = 7.9, 7.6, 6.9, 3.3 Hz, H-3), 3.36 (1H, dq, J = 6.9, 6.8 Hz, H-6), 2.83 (1H, d, J = 7.6 Hz, 3-OH), 2.75 (1H, ddd, J = 16.1, 6.6, 3.4 Hz, H-14a), 2.74 (1H, dd, J = 15.3, 3.3 Hz, H-2a), 2.71 (3H, s, H-21), 2.58 (2H, m, H-14b and H-8), 2.50 (1H, dd, J = 15.3, 7.9 Hz, H-2b), 2.29 (1H, m, H-11a), 2.10 (1H, m, H-11b), 2.09 (3H, d, J = 0.7 Hz, H-27), 1.78 (1H, m, H-9a), 1.65 (1H, m, H-10a), 1.48 (1H, m, H-10b), 1.18 (1H, m, H-9b), 1.15 (3H, d, J = 6.8 Hz, H-22), 1.03 (3H, d, J = 6.5 Hz, H-25); EIMS *m/z* 405 $[M]^+$ (38), 317 (12), 260 (9), 232 (10), 204 (14), 190 (16), 168 (100), 164 (30), 151 (28); HREIMS *m/z* 405.XXX (calcd. for $C_{26}H_{39}NO_5S$, 405.XXX).

(37): colorless amorphous solid; $[\alpha]^{22}_D$ –27.5 (*c* 0.4, MeOH); UV (MeOH) λ_{max} nm (ε)

211 (16100), 247 (12100); IR (KBr) ν_{max} 3431, 2967, 2929, 2875, 1704, 1462, 1381, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.94 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.56 (1H, dtt, *J* = 10.8, 7.3, 1.4 Hz, H-12), 5.39 (1H, dtt, *J* = 10.8, 7.3, 1.4 Hz, H-13), 4.17 (1H, t, *J* = 6.6 Hz, H-15), 3.50 (1H, ddd, *J* = 8.7, 2.6, 2.6 Hz, H-7), 3.10 (1H, d, *J* = 2.6, 7-OH), 2.90 (1H, dq, *J* = 2.6, 7.2 Hz, H-6), 2.77 (1H, sep, *J* = 6.9 Hz, H-4), 2.70 (3H, s, H-21), 2.40 (2H, m, H-14), 2.07 (2H, m, H-11), 2.04 (3H, d, *J* = 1.1 Hz, H-27), 1.78 (1H, bs, 15-OH), 1.74 (1H, m, H-9a), 1.50 (1H, m, H-8), 1.46 (1H, m, H-10a), 1.27 (1H, m, H-10b), 1.11 (1H, m, H-9b), 1.094 (3H, d, *J* = 6.9 Hz, H-23), 1.089 (3H, d, *J* = 6.9 Hz, H-22), 1.08 (3H, d, *J* = 7.2 Hz, H-24), 0.82 (3H, d, *J* = 6.7 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.5 (s, C-5), 164.6 (s, C-20), 152.9 (s, C-18), 141.5 (s, C-16), 133.4 (d, C-12), 125.0 (d, C-13), 119.2 (d, C-17), 115.6 (d, C-19), 77.2 (d, C-15), 74.9 (d, C-7), 44.9 (d, C-6), 40.0 (d, C-4), 35.5 (d, C-8), 33.5 (t, C-14), 32.3 (t, C-9), 27.9 (t, C-11), 26.9 (t, C-10), 19.2 (q, C-21), 18.6 (q, C-23), 18.1 (q, C-22), 15.6 (q, C-25), 14.4 (q, C-27), 9.3 (q, C-24); EIMS *m/z* 407 $[M]^+$ (0.1), 204 (0.8), 168 (100), 140 (3.4); HREIMS *m/z* 407.XXX (calcd. for $C_{23}H_{37}NO_3S$, 407.XXX).

(38): colorless amorphous solid; $[\alpha]^{22}_D$ +25.0 (*c* 0.5, MeOH); UV (MeOH) λ_{max} nm (ε) 212 (17700), 247 (13400); IR (KBr) ν_{max} 3427, 2971, 2933, 2878, 2858, 1709, 1457, 1377, 1186, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.52 (1H, dtt, *J* = 10.9, 7.2, 1.4 Hz, H-12), 5.39 (1H, dtt, *J* = 10.9, 7.1, 1.2 Hz, H-13), 4.18 (1H, ddt, *J* = 3.4, 0.4, 6.7 Hz, H-15), 2.71 (3H, s, H-21), 2.51 (1H, bq, *J* = 6.8 Hz, H-8), 2.48 (1H, dq, *J* = 17.7, 7.4 Hz, H-6a), 2.41 (1H, dq, *J* = 17.7, 7.2 Hz, H-6b), 2.39 (2H, ddd, *J* = 7.1, 6.7, 1.4 Hz, H-14), 2.06 (2H, ddt, 7.2, 1.2, 7.0 Hz, H-11), 2.05 (3H, d, *J* = 1.4 Hz, H-27), 1.81 (1H, d, *J* = 3.4 Hz,

15-OH), 1.66 (1H, m, H-9a), 1.32 (1H, m, H-9b), 1.31 (2H, m, H-10), 1.06 (3H, d, J = 6.9 Hz, H-25), 1.04 (3H, dd, J = 7.4, 7.2 Hz, H-24); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.3 (s, C-7), 164.6 (s, C-20), 152.9 (s, C-18), 141.5 (s, C-16), 132.7 (d, C-12), 125.3 (d, C-13), 119.2 (d, C-17), 115.6 (d, C-19), 77.2 (d, C-15), 46.0 (d, C-8), 34.3 (t, C-14), 33.5 (t, C-6), 32.7 (t, C-9), 27.5 (t, C-11), 27.3 (t, C-10), 19.2 (q, C-21), 16.5 (q, C-25), 14.4 (q, C-27), 7.8 (q, C-24); EIMS *m/z* 335 $[M]^+$ (2), 317 (4), 170 (27), 169 (67), 168 (100), 140 (20); HREIMS *m/z* 335.1912 (calcd. for $C_{19}H_{29}NO_2S$, 335.1919).

(39): colorless amorphous solid; $[\alpha]^{22}_D$ +26.4 (*c* 0.27, MeOH); UV (MeOH) λ_{max} nm (ε) 203 (19100), 244 (12500); IR (KBr) ν_{max} 3430, 2970, 2934, 2877, 1710, 1458, 1377, 1184 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.94 (1H, s, H-19), 6.55 (1H, bs, H-17), 5.17 (1H, t, J = 7.3 Hz, H-13), 4.13 (1H, m, H-15), 2.70 (3H, s, H-21), 2.51 (1H, bq, J = 6.8 Hz, H-8), 2.47 (1H, dq, J = 17.7, 7.2 Hz, H-6a), 2.41 (1H, dq, J = 17.7, 7.2 Hz, H-6b), 2.33 (2H, bdd, J = 7.3, 6.8 Hz, H-14), 2.05 (3H, d, J = 1.2 Hz, H-27), 2.03 (2H, m, H-11), 1.71 (1H, d, J = 3.2 Hz, 15-OH), 1.69 (3H, d, J = 1.3 Hz, H-26), 1.62 (1H, m, H-9a), 1.32 (3H, m, H-10 and H-9b), 1.06 (3H, d, J = 6.9 Hz, H-25), 1.03 (3H, t, J = 7.2 Hz, H-24); EIMS *m/z* 349 $[M]^+$ (0.7), 331 (1.7), 168 (100), 140 (5.1); HREIMS *m/z* 349.XXX (calcd. for $C_{20}H_{31}NO_2S$, 349.XXX).

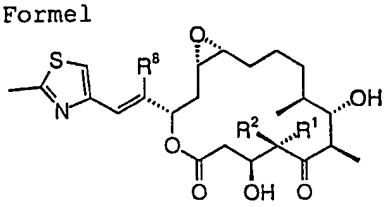
Tab 1. Aktivität von Epothilonen und Verbindungen (1) bis (39) gegen Maus-Fibroblasten (L929, IC50 /ng/ml/)

Struktur-typ	Epothilone				
	A_Y	B_Y	C_Y	D_Y	trans C_Y
Ausgangs-epothilon	(1) 4	(2) 1-2	(14) 50-100	(15) 20	-
21-Hydroxy (E&F)	(3) 10	(4) 1.5	-	-	-
Oxazoles (G&H)	(10) 6	(11) 1	(12) 120	(13) 11	-
(R)-4-Desmethyl (X_1)	(5) 20	-	(16) 200	(17) 20	(28) 400
(S)-4-Desmethyl (X_2)	(6) 7	-	(18) 25-30	(19) 12	(29) 80
6-Desmethyl (X_3)	-	-	(20) 1500	-	-
8-Desmethyl (X_4)	-	-	(21) 800	-	-
8,9-Dehydro (X_5)	-	-	(22) 1500	(23) 200	-
10,11-Dehydro (X_6)	-	-	(24) 120	-	-
14-Hydroxy (X_7)	-	-	(25)	-	-
16-Desmethyl (X_8)	(7) 20	-	(26) 250	-	-
27-Hydroxy (X_9)	(8) 100	-	(27) 200	-	-
21-Methyl (X_{10})	-	(9) 1.5	-	-	-
Verbindung	-	-	(36) 180		
Verbindung	-	-	(37) 50	-	-
Verbindung	-	-	(38) 2000	(39) 500	-

Epothilon-Nebenkomponenten

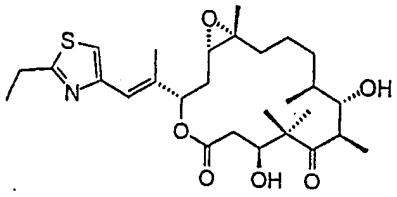
Patentansprüche

1. Epothilon der Formel



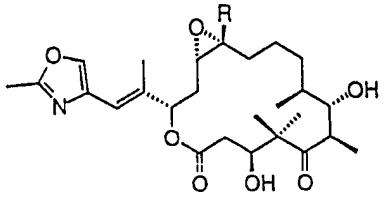
Epothilone A_1 (5) $R^1 = H$; R^2, $R^8 = Me$
Epothilone A_2 (6) $R^2 = H$; R^1, $R^8 = Me$
Epothilone A_8 (7) $R^8 = H$; R^1, $R^2 = Me$ oder
Epothilone A_9 (8) $R^1 = CH_2OH$; R^2, $R^8 = Me$

2. Epothilon der Formel



Epothilone B_{10} (9)

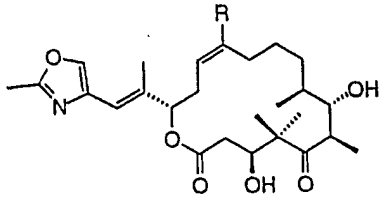
3. Epothilon der Formel



- ✓ Epothilone G_1 **(10)** R = H
- ✓ Epothilone G_2 **(11)** R = Me

oder

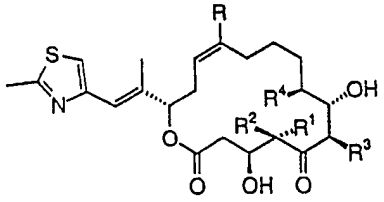
4. Epothilon der Formel



- ✓ Epothilone H_1 **(12)** R = H
- ✓ Epothilone H_2 **(13)** R = Me

oder

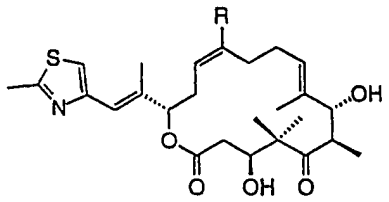
5. Epothilon der Formel



- ✓ Epothilone C_1 **(16)** R^1 = H; R^2, R^3, R^4 = Me; R = H
- ✓ Epothilone D_1 **(17)** R^1 = H; R^2, R^3, R^4 = Me; R = Me
- ✓ Epothilone C_2 **(18)** R^2 = H; R^1, R^3, R^4 = Me; R = H
- ✓ Epothilone D_2 **(19)** R^2 = H; R^1, R^3, R^4 = Me; R = Me
- ✓ Epothilone C_3 **(20)** R^3 = H; R^1, R^2, R^4 = Me; R = H
- ✓ Epothilone C_4 **(21)** R^4 = H; R^1, R^2, R^3 = Me; R = H

oder

6. Epothilon der Formel

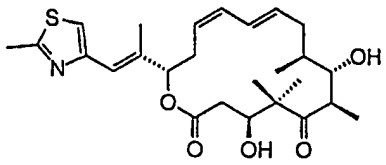


Epothilone C_5 (22) R = H

Epothilone D_5 (23) R = Me

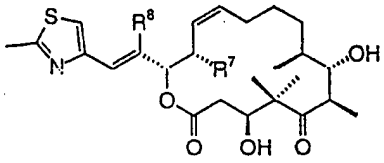
oder

7. Epothilon der Formel



✓ Epothilone C_6 (24)

8. Epothilin der Formel



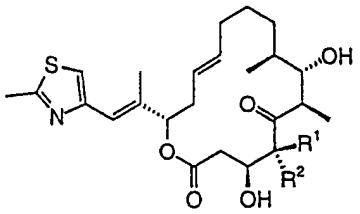
✓ Epothilone C_7 (25) R^7 = OH; R^8 = Me

✓ Epothilone C_8 (26) R^8, R^7 = H

✓ Epothilone C_9 (27) R^8 = CH_2OH; R^7 = H

oder

9. Epothilon der Formel

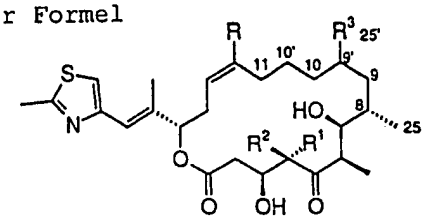


✓ trans-Epothilone C_1 (28) R^1 = H; R^2 = Me

✓ trans-Epothilone C_2 (29) R^2 = H; R^1 = Me

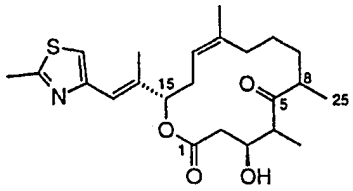
oder

10. Epothilon der Formel



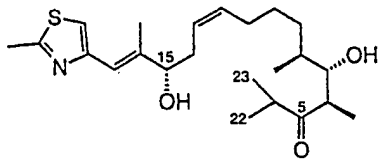
Epothilone I_1 (30) R, R^3 = H; R^1, R^2 = Me
Epothilone I_2 (31) R = H; R^1, R^2, R^3 = Me
Epothilone I_3 (32) R^1, R^2, R^3, R = Me
Epothilone I_4 (33) R^2, R = H; R^1, R^3 = Me
Epothilone I_5 (34) R^2 = H; R^1, R^3, R = Me oder
Epothilone I_6 (35) R^1 = H; R^2, R^3, R = Me

11. Epothilon der Formel



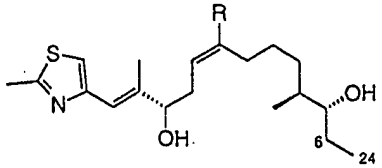
Epothilone K (36)

12. Verbindung der Formel



(37)

13. Verbindung der Formel



(38) R = H oder
(39) R = Me

Fig. 1

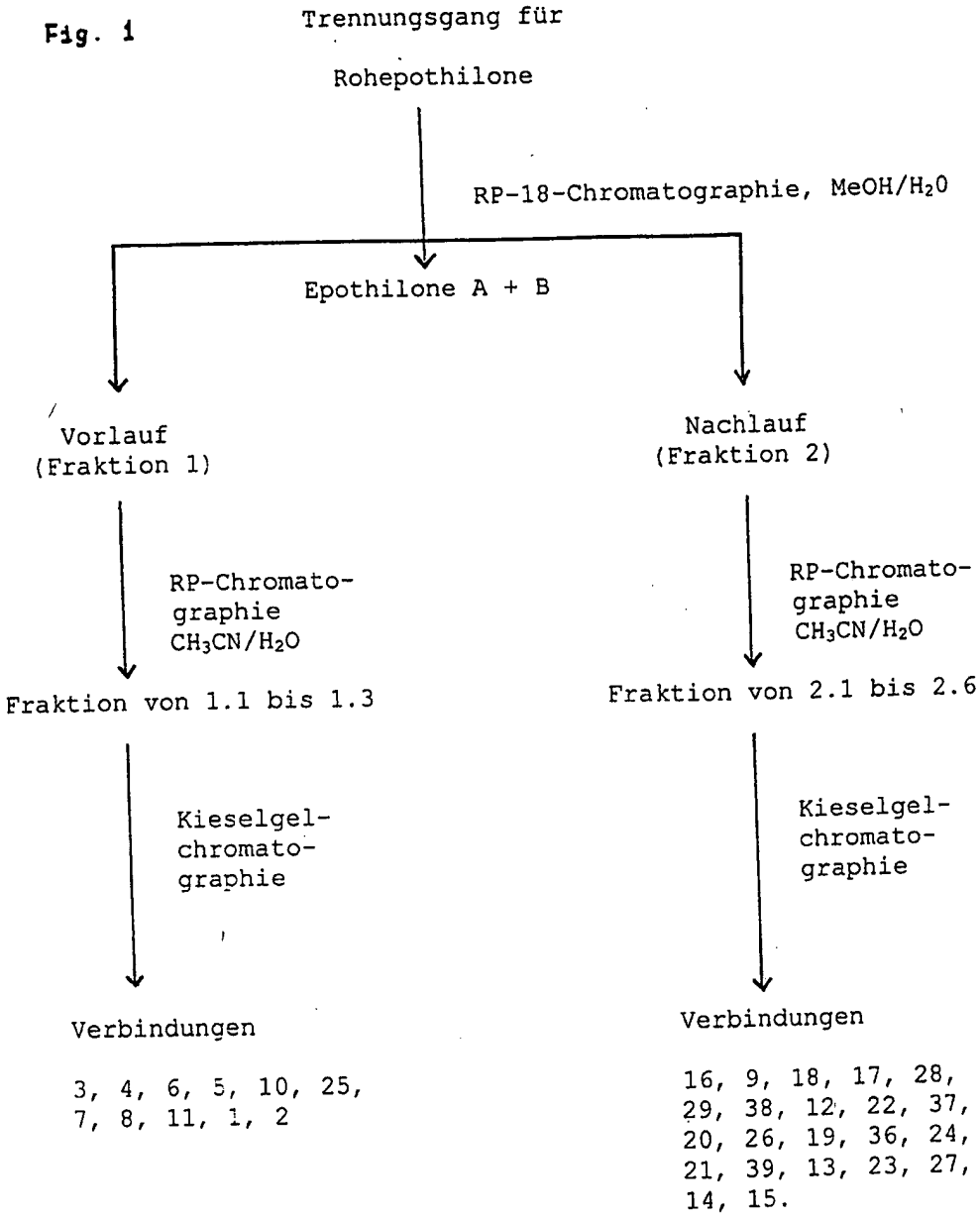
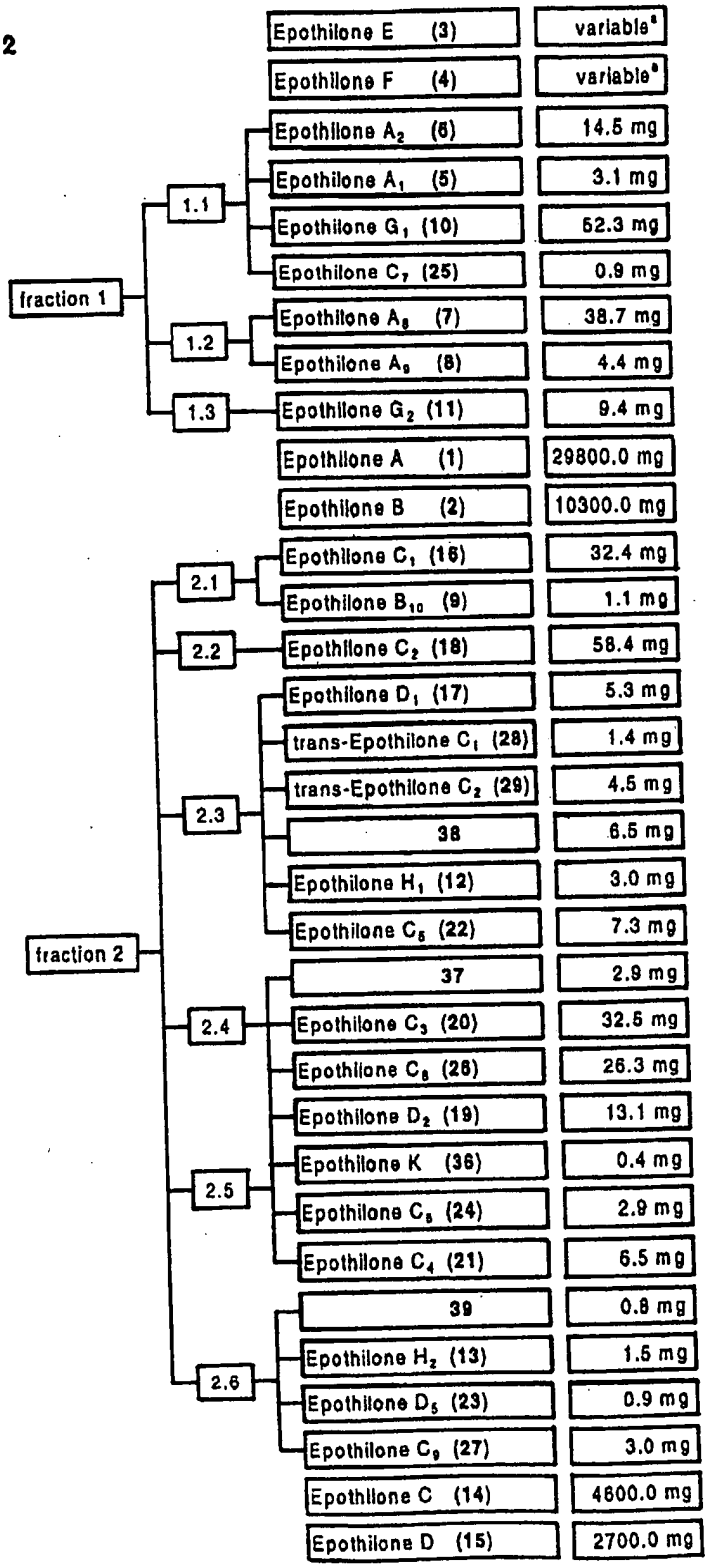

Trennungsgang für
Rohepothilone
RP-18-Chromatographie, MeOH/H2O
Epothilone A + B
Vorlauf
(Fraktion 1)
Nachlauf
(Fraktion 2)
RP-Chromato-
graphie
CH3CN/H2O
RP-Chromato-
graphie
CH3CN/H2O
Fraktion von 1.1 bis 1.3
Fraktion von 2.1 bis 2.6
Kieselgel-
chromato-
graphie
Kieselgel-
chromato-
graphie
Verbindungen
3, 4, 6, 5, 10, 25,
7, 8, 11, 1, 2
Verbindungen
16, 9, 18, 17, 28,
29, 38, 12, 22, 37,
20, 26, 19, 36, 24,
21, 39, 13, 23, 27,
14, 15.

Fig. 2


fraction 1
1.1
1.2
1.3
fraction 2
2.1
2.2
2.3
2.4
2.5
2.6
Epothilone E (3)
variable[a]
Epothilone F (4)
variable[a]
Epothilone A2 (6)
14.5 mg
Epothilone A1 (5)
3.1 mg
Epothilone G1 (10)
52.3 mg
Epothilone C7 (25)
0.9 mg
Epothilone A3 (7)
38.7 mg
Epothilone A4 (8)
4.4 mg
Epothilone G2 (11)
9.4 mg
Epothilone A (1)
29800.0 mg
Epothilone B (2)
10300.0 mg
Epothilone C1 (16)
32.4 mg
Epothilone B10 (9)
1.1 mg
Epothilone C2 (18)
58.4 mg
Epothilone D1 (17)
5.3 mg
trans-Epothilone C1 (28)
1.4 mg
trans-Epothilone C2 (29)
4.5 mg
38
6.5 mg
Epothilone H1 (12)
3.0 mg
Epothilone C5 (22)
7.3 mg
37
2.9 mg
Epothilone C3 (20)
32.5 mg
Epothilone C6 (26)
26.3 mg
Epothilone D2 (19)
13.1 mg
Epothilone K (36)
0.4 mg
Epothilone C5 (24)
2.9 mg
Epothilone C4 (21)
6.5 mg
39
0.8 mg
Epothilone H2 (13)
1.5 mg
Epothilone D5 (23)
0.9 mg
Epothilone C9 (27)
3.0 mg
Epothilone C (14)
4600.0 mg
Epothilone D (15)
2700.0 mg

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 :
C07D 493/04, 417/06, 413/06, 277/24
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(30) Prioritätsdaten:
198 26 988.9 18. Juni 1998 (18.06.98) DE

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(74) Anwälte: BOETERS, Hans usw.; Boeters & Bauer, Bereiteranger 15, D–81541 München (DE).

(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 20. April 2000 (20.04.00)

(54) Title: EPOTHILONE MINOR CONSTITUENTS

(54) Bezeichnung: EPOTHILON–NEBENKOMPONENTEN

(57) Abstract

The invention relates to compounds which are obtained by fermenting DSM 6773, especially epothilones A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 and K and trans–epothilones C1 and C2.

(57) Zusammenfassung

Die Erfindung betrifft Verbindungen, die durch Fermentation von DSM 6773 erhältlich sind, insbesondere Epothilone A1, A2, A8, A9, B10, C1, C2, C3, C4, C5, C6, C7, C8, C9, D1, D2, D5, G1, G2, H1, H2, I1, I2, I3, I4, I5, I6 und K und Trans–Epothilone C1 und C2.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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EE	Estland	LR	Liberia	SG	Singapur		

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP 99/04244

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D493/04 C07D417/06 C07D413/06 C07D277/24
//(C07D493/04,313:00,303:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT ;BAUER ARMIN (DE); CORDES MARTIN (DE);) 5 March 1998 (1998-03-05) abstract; claims; examples	1-13
X	WO 98 22461 A (BIOTECHNOLOG FORSCHUNG GMBH ;GERTH KLAUS (DE); HOEFLE GERHARD (DE)) 28 May 1998 (1998-05-28) abstract; claims; examples	1-13
X	WO 97 19086 A (BIOTECHNOLOG FORSCHUNG GMBH ;KIFFE MICHAEL (DE); HOEFLE GERHARD (D) 29 May 1997 (1997-05-29) abstract; claims; examples	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2000	07/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Paisdor, B

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INTERNATIONAL SEARCH REPORT

Internation pplication No
PCT/EP 99/04244

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	NICOLAOU K C ET AL: "DESIGNED EPOTHILONES: COMBINATORIAL SYNTHESIS, TUBULIN ASSEMBLY PROPERTIES, AND CYTOTOXIC ACTION AGAINST TAXOL.RESISTANT TUMOR CELLS" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, vol. 36, no. 19, 1 January 1997 (1997-01-01), pages 2097-2103, XP002064441 ISSN: 0570-0833 page 2099 -page 2100	1-13
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X	BALOG A ET AL: "Stereoselective Syntheses and Evaluation of Compounds in the 8-Desmethylepothilone A Series: Some Surprising Observations Regarding Their Chemical and Biological Properties" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 38, no. 26, 30 June 1997 (1997-06-30), pages 4529-4532, XP004074826 ISSN: 0040-4039 the whole document	1-13
X	SU D -S ET AL: "STRUCTURE - ACTIVITY RELATIONSHIPS OF THE EPOTHILONES AND THE FIRST IN VIVO COMPARISON WITH PACLITAXEL" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, vol. 36, no. 19, 1997, pages 2093-2096, XP002916075 ISSN: 0570-0833 page 2094 -page 2095	1-13

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INTERNATIONAL SEARCH REPORT

Internation Application No
PCT/EP 99/04244

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K.C. NICOLAOU ET AL.: "Probing the ring size of epothilones: total synthesis of '14!-, '15!-, '17!-, and '18!Epothilones A" ANGEWANDTE CHEMIE INTERNATIONAL EDITION., vol. 37, no. 1/2, 1998, pages 81-84, XP002131226 WEINHEIM DE the whole document	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio application No
PCT/EP 99/04244

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WO 9808849 A	05-03-1998	DE 19636343 C	23-10-1997
		DE 19645361 A	30-04-1998
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		AU 2149397 A	19-03-1998
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		CZ 9901750 A	15-09-1999
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INTERNATIONALER RECHERCHENBERICHT

Internation. Aktenzeichen
PCT/EP 99/04244

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 C07D493/04 C07D417/06 C07D413/06 C07D277/24
//(C07D493/04,313:00,303:00)

Nach der internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 C07D

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT ;BAUER ARMIN (DE); CORDES MARTIN (DE);) 5. März 1998 (1998-03-05) Zusammenfassung; Ansprüche; Beispiele	1-13
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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
22. Februar 2000	07/03/2000

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Paisdor, B

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INTERNATIONALER RECHERCHENBERICHT

Internatio[illegible] Aktenzeichen
PCT/EP 99/04244

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	NICOLAOU K C ET AL: "DESIGNED EPOTHILONES: COMBINATORIAL SYNTHESIS, TUBULIN ASSEMBLY PROPERTIES, AND CYTOTOXIC ACTION AGAINST TAXOL.RESISTANT TUMOR CELLS" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, Bd. 36, Nr. 19, 1. Januar 1997 (1997-01-01), Seiten 2097-2103, XP002064441 ISSN: 0570-0833 Seite 2099 -Seite 2100	1-13
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X	SU D -S ET AL: "STRUCTURE - ACTIVITY RELATIONSHIPS OF THE EPOTHILONES AND THE FIRST IN VIVO COMPARISON WITH PACLITAXEL" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, Bd. 36, Nr. 19, 1997, Seiten 2093-2096, XP002916075 ISSN: 0570-0833 Seite 2094 -Seite 2095	1-13

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C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

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